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REVIEW

Dasatinib-induced pulmonary arterial hypertension

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Drug-induced (group 1) pulmonary hypertension (PH) is an important subgroup of PH involving dasatinib as a likely related agent, which is a second-generation tyrosine kinase inhibitor (TKI) used in the treatment of chronic myeloid leukaemia (CML). The mechanism of dasatinib-induced pulmonary arterial hypertension (PAH) is unclear. However, the occurrence of PAH with late onset in CML patients suggests a chronic pathological mechanism with an insidious onset rather than an acute inflammatory or cardiac aetiology. Dasatinib has a broader effect than other TKIs; the major known difference between dasatinib and other TKIs is the additional inhibition of Src family kinases. Therefore, Src inhibition was thought to play a role in the development of dasatinib-induced PAH. However, recently, it was also speculated that chronic dasatinib therapy may cause pulmonary endothelial damage, attenuate hypoxic pulmonary vasoconstriction responses and increase susceptibility to PAH independently of the Src family kinase-induced mechanism. Dasatinib-induced PAH usually seems to be reversible with the cessation of the drug, and sometimes with PAH-specific treatment strategies. Transthoracic echocardiography can be recommended as a routine screening prior to dasatinib initiation, and this non-invasive procedure can be utilized in patients having signs and symptoms attributable to PAH during dasatinib treatment.

Introduction

Pulmonary hypertension (PH) is elevated pulmonary arterial pressure (PAP), above the normal meal value of 14 ± 3 mmHg. It is defined as a mean PAP (mPAP) ≥25 mmHg at rest, usually confirmed by right heart catheterization (RHC), and may lead to an increase in pulmonary vascular resistance and right heart failure, which can be progressive, and even fatal if left untreated [1–4]. PH should be considered in patients with exertional dyspnoea, fatigue, atypical chest pain and unexplained syncope, and it may be suspected if the right ventricular systolic pressure, which is equal to the pulmonary arterial systolic pressure in the absence of pulmonary outflow obstruction, is high. The estimation of systolic PAP is based on the peak tricuspid regurgitation velocity (TRV), taking into account right atrial pressure (RAP) as described by an equation that is based on the diameter and respiratory variation in the diameter of the inferior vena cava [2, 5]. However, conclusions derived from an echocardiographic examination should aim to assign the level of probability of PH as high, intermediate and low risk in order to guide clinicians as to whether or not to perform RHC [6, 7].

There is still no specific marker for PH, although a wide variety of biomarkers have been explored in the field [6]. This list of biomarkers is constantly growing, but so far brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) remain the only markers that are widely used in daily clinical practice. Although they are not specific for PH, plasma levels of BNP/NT-proBNP should be measured at initial evaluation as well as during the follow-up [6, 8, 9]. Plasma levels of BNP/NT-proBNP may correlate with prognosis; low-risk patients have a BNP <50 ng l^{-1} and/or NT-proBNP <300 ng l^{-1}, whereas in high-risk patients BNP and NT-proBNP are usually found to be >300 ng l^{-1} and >1400 ng l^{-1}, respectively [6].

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PH can be classified into five groups according to pathomechanisms and clinical management [10]. Group 1 PH, also called pulmonary arterial hypertension (PAH), includes precapillary PH [with a normal pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and a pulmonary vascular resistance >3 Wood units in the absence of other causes of precapillary PH, such as PH due to lung diseases, chronic thromboembolic PH (CTEPH) or other rare diseases] that can be idiopathic, heritable or drug induced, or associated with connective tissue diseases, human immunodeficiency syndrome, portal hypertension, schistosomiasis or congenital heart diseases. Group 2 corresponds to postcapillary PH; group 3 corresponds to PH due to chronic lung disease or hypoxia; and group 4 corresponds to CTEPH and other causes of pulmonary artery obstruction. Group 5 consists of several forms of PH, for which pathogenesis is unclear or multifactorial, including PH related to myeloproliferative neoplasms (MPNs) [1, 4, 10].

Three distinct clinical forms of PH have been described in patients with MPNs: CTEPH, precapillary PH and drug-induced PAH [11–15]. Precapillary PH is usually diagnosed late in the course of the haematological disease, while CTEPH is usually diagnosed earlier and may even be concurrent with the haematological diagnosis. High haematocrit levels with hyperviscosity, thrombocytosis and splenectomy, among other mechanisms, may contribute to the increased rate of thrombotic events in patients with MPN, especially polycythaemia vera. PAH-like disease associated with MPN was found to be related to myeloid metaplasia, suggesting that pulmonary myeloid infiltration and pulmonary capillary obstruction by megakaryocytes with stasis and secondary microthrombosis may contribute to the pulmonary vascular disease. Treatment of MPN-associated PH is not yet well established, although cytoreductive treatment should be used in association with symptomatic treatment of PH, such as oxygen and diuretics. The prognosis of PH associated with MPN remains poor, and there are no data on the effectiveness of specific PAH therapies in these patients [11–15].

Treatment of secondary PH (groups 2–5) includes oxygen, anticoagulation (usually in group 4 and some of the subgroups of PAH) and diuretics, together with the management of the underlying aetiology [5, 16, 17]. Although these supportive therapies and/or calcium channel blockers after a positive acute vasodilator testing are used effectively, only a small number of patients with PAH demonstrate a favourable response with these treatment modalities [6, 18]. As a result, advanced PAH-specific therapy, including prostanoids (epoprostenol, iloprost, treprostinil, beraprost and selexipag), endothelin receptor antagonists (ambrisentan, bosentan, macitentan), phosphodiesterase 5 inhibitors (sildenafil, tadalafil, vardenafil, riociguat), guanylate cyclase stimulants and combination therapy, is often needed [16, 17, 19–21].

PH is generally a progressive condition, and is sometimes fatal, if left untreated. The prognosis of PH is highly variable and depends upon the type and severity of PH. In general, in the absence of therapy, those with group 1 PAH have worse survival than those with groups 2–5, with the exception of patients with surgically correctable CTEPH (group 4). In general, those with severe PH (e.g. mPAP ≥35 mmHg) and/or evidence of right heart failure have a poorer prognosis [22, 23].

In the present review, we discuss a specific subgroup of PAH – so called 'drug-induced PAH' – and then focus mainly on the current knowledge on **dasatinib**-induced PAH.

Chronic myeloid leukaemia (CML) and tyrosine kinase inhibitors (TKIs)

CML is a haematopoietic stem cell disease characterized by a translocation between chromosomes 9 and 22, and the Philadelphia (Ph) chromosome is formed by the fusion of the breakpoint cluster region (*BCR*) and the Abelson murine leukaemia (*ABL1*) genes. The resulting *BCR-ABL1* fusion gene leads to an ABL protein that forms a constitutively active tyrosine kinase protein, with cell-cycle deregulation [24, 25]. The mainstay of CML treatment is currently based on targeted therapy with TKIs [26, 27]. Imatinib was the first TKI to be approved for the treatment of CML. Although many patients have good responses with this drug, some can become resistant and/or intolerant to it [26, 28]. Second-generation TKIs (dasatinib and nilotinib) were subsequently introduced, to provide greater efficacy in patients who were resistant or intolerant to imatinib, and have also been used in the frontline setting [26, 29, 30]. Two other TKIs, bosutinib and ponatinib, have recently been approved by the Food and Drug Administration (FDA) only for second- or later-line therapies [31].

Dasatinib is 325 times more potent *in vitro* against unmutated *BCR-ABL1* than imatinib [32]. It is indicated for the treatment of CML and Ph + acute lymphoblastic leukaemia (ALL) after imatinib failure/intolerance, and this has recently been expanded to the frontline setting. It is metabolized mainly in the liver. Although it is usually well tolerated, it is associated with some adverse events (AEs), including bone marrow suppression, diarrhoea, skin rash, pleural/pericardial effusions and, rarely, PAH, QT prolongation and bleeding tendency [26, 33–35]. In addition to *BCR-ABL1*, TKIs may inhibit a large number of other kinases. For example, dasatinib inhibits many other targets, including the **Src family** kinases, which are thought to be associated with some of the nonhaematological AEs [33, 36].

Dasatinib and pulmonary toxicities

At the previously recommended dose of 70 mg twice per day, one of the most relevant nonhaematological AEs, the so called 'off-target effects', of dasatinib was exudative pleural effusion (PE), which has been observed in up to 14–35% of patients, and has been related to an autoimmune-mediated mechanism or inhibition of platelet-derived growth factor receptor (PDGFR) β, as opposed to fluid retention [37–39]. However, the occurrence of grade III–IV PE has decreased to less than 2% at the presently approved dosage of 100 mg once per day [31, 37–39]. The current recommended dose of dasatinib for advanced CML and Ph + ALL is 140 mg per day, and 100 mg per day for chronic-phase CML (CML-CP). It has been found that PEs can also occur in imatinib-

intolerant/resistant CML patients treated with smaller doses of dasatinib (i.e. 50 mg daily) [40]. However, PE generation under second-line dasatinib can be associated with superior outcomes [41]. Other AEs involving the cardiopulmonary system and the lungs are heart failure, QTc prolongation, pericardial effusion, pulmonary parenchymal infiltrates and PAH [2, 34, 42, 43].

Drug-induced PAH

Drug-induced PAH was first introduced to the literature associated with intake of an anorectic agent, aminorex, in 1965 in Switzerland, Germany and Austria [44, 45]. After that, improvement in medical awareness and diagnosis of the disease allowed the identification of additional drugs associated with an increased risk for the development of PAH. In the European Respiratory Society/European Society of Cardiology guidelines for the diagnosis and treatment of PAH, drugs and toxins are classified into four categories based on their risk of inducing PAH (Table 1) [6]. At the beginning of the 21st century, drug-associated PAH is still a clinical problem. It remains a great challenge to confirm that a drug is responsible for PAH because the latter is always a rare complication, occurring in only a small proportion of exposed patients (usually 1%) [46, 47]. Although the mechanism of drug-induced PH remains unclear, it was thought that serotonin might play a role in the generation of this phenomenon [46]. The most important aspect of management of drug-induced PAH is cessation of the associated drug. However, some drugs, such as anorectic agents, usually cause irreversible PAH, unlike dasatinib, and PAH related to these agents may be detected several months or years after cessation of the drug.

Dasatinib and PAH

Dasatinib is considered to be one of the causes of group 1 drug-induced PH [10]. PAH can be observed during the course of dasatinib treatment and may be related directly to use of this drug. However, other causes of PAH, such as congenital heart disease, chronic pulmonary embolism and left heart failure, must be ruled out before ascribing this condition to use of the drug. Although complete resolution of PAH does not always occur after discontinuation of dasatinib, it is reasonable to assume that a diagnosis of dasatinib-induced PAH is possible whenever any improvement is observed after cessation of the drug. Table 2 presents the published cases of dasatinib-induced PAH in the English-language literature.

A study by Quintas-Cardama and coworkers [37] in 138 dasatinib-treated patients, found increased right ventricular systolic pressure in 18 of them [who underwent transthoracic echocardiography (TTE) at the onset of pleural effusion], from a median of 29 (range 21–44) mmHg at baseline to a median of 42 (range 25–75) mmHg, with a return to baseline levels after discontinuation of the drug. Thus, the authors suggested, for the first time, that there might be an association between dasatinib and PAH [37]. Then, in October 2011, the FDA issued a drug safety communication concerning dasatinib, warning about the risk of PAH [48, 49]. Then, in 2012, Montani *et al*. [4] published a case series consisted of eight CML and one Ph + ALL patient with dasatinib-induced PAH from the French Registry Network. The median delay between initiation of dasatinib and PAH diagnosis was 34 months (range, 8–48 months), suggesting that PAH may be a late complication of dasatinib. Clinical and functional improvements were usually observed after cessation of dasatinib; however, some patients also required specific PAH treatment. Our group reported a case series consisting of five patients with dasatinib-related PAH [50]. We noted that PAH was almost completely reversible in all cases, following a reduction in the dasatinib dose in two patients and drug cessation in three, and none of them needed PAH-specific therapies. However, unlike the case reports suggesting almost complete recovery with drug cessation together with specific PAH treatment strategies (such as bosentan or sildenafil), the majority of patients have failed to demonstrate complete haemodynamic recovery, and two patients have died during follow-up [3, 4, 51, 52]. Moreover, recently, Morishita and colleagues [53] published a paper which described the first death directly related to dasatinib-induced PAH. A 36-year-old woman with CML received dasatinib for 34 months and died of cardiac arrest 4 days after presenting with severe PAH and right heart failure, despite the use of catecholamines and phosphodiesterase inhibitors. Montani *et al*. [4] estimated that the lowest incidence of PAH in patients exposed to dasatinib was 0.45%. Although PAH is thought to be a delayed complication of dasatinib in CML patients, in the Ph + ALL patient from the French registry, PAH developed earlier (after 8 months of dasatinib) [4]. In addition, two other case reports have observed earlier PAH development related to dasatinib, with a dose of 140 mg per day, in two Ph + ALL patients [52, 54]. Although the mechanism for earlier development of this condition is unclear, Kim and colleagues [52] suggested that it may be associated with the combined effects of cytotoxic chemotherapy and dasatinib in Ph + ALL patients. Dasatinib was used as second-line or later therapy in almost all CML and Ph + ALL cases in the literature

Table 1

Drugs and toxins that might play a role in the generation of pulmonary arterial hypertension (adapted from Montani *et al*. [3])

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

Table 2

Cases published in the literature demonstrating dasatinib-induced pulmonary arterial hypertension

First author, year and reference No.[a]	No. of patients	Age, years/ gender, M/F	Diagnosis	Time from DAS initiation to PAH, months	DAS dose, mg day^{-1}	Treatment line of DAS	Treatments prior to DAS	Tool used in diagnosis of PAH	Accompanying PE	Treatment of PAH	Outcome of PAH
Rasheed *et al.*, 2009 [2]	1	41/M	CML	26	2×70	2nd	HU + IM	RHC	Yes	DAS cessation	Reversible
Montani *et al.*, 2012 [4]	9	Median age: 51 (17–74) 8F/1M	8➔CML 1➔Ph + ALL	8–48	70–140	2nd and 3rd	IFN-α, HU, 6-MP, Ara-C, IM, VCR + MTX + ADR + Ara-C	RHC	3 ➔ No 6 ➔ Yes	DAS cessation + BOS (in 2 patients)	Reversible –not complete (except one patient)
Orlandi *et al.*, 2012 [34]	1	53/F	CML	31	100	2nd	IM	RHC	No	DAS cessation + SIL	Reversible
Mattei *et al.*, 2009 [42]	1	48/M	CML	19	2×70	3rd	IFN-α, Allo-HSCT, IM	TTE	Yes	DAS cessation	Reversible
Hennings *et al.*, 2011 [43]	1	70/M	CML	32	2×70	3rd	HU + IFN-α, IM	RHC	Yes	DAS cessation + SIL	Reversible
Sano *et al.*, 2012 [49]	1	61/F	CML	27	140	2nd	IM	RHC	Yes	DAS cessation + SIL	Reversible
Wang *et al.*, 2015 [51]	1	33/M	CML	63	100	2nd	HU + IM	TTE	No	DAS cessation + SIL	Reversible
Kim *et al.*, 2013 [52]	1	24/M	Ph + ALL	0.3	140	2nd	VCR, DAU, L-asp, PRED	TTE	Yes	DAS cessation	Reversible
Taçoy *et al.*, 2015 [54]	1	50/M	Ph + ALL	24	140	2nd	Hyper CVAD + IM, FLAG Ida,	RHC	Yes	DAS cessation + BOS	Reversible
Dumitrescu *et al.*, 2011 [57]	1	47/M	CML	39	100	3rd	PegIFN-α, IM	RHC	Yes	DAS cessation + SIL	Reversible
Groeneveldt *et al.*, 2013 [68]	1	57/M	CML	37	70	2nd	IM	RHC	No	DAS cessation + SIL	Reversible
Yun *et al.*, 2014 [69]	1	46/F	CML	3	NR	2nd	IM	TTE	No	DAS cessation	Reversible
Hong *et al.*, 2015 [70]	2	43/M	CML	69	140	2nd	IM	TTE	Yes	DAS cessation + SIL	Reversible
		52/M	CML	26	140	3rd	IFN-α, IM	TTE	No	DAS cessation + SIL	Reversible
Buchelli Ramirez *et al.*, 2014 [71]	1	50/M	CML	48	100	2nd	IM	RHC	Yes	DAS cessation + SIL	Reversible

(*continues*)

Table 2

(Continued)

First author, year and reference No.[a]	No. of patients	Age, years/ gender, M/F	Diagnosis	Time from DAS initiation to PAH, months	DAS dose, mg day^{-1}	Treatment line of DAS	Treatments prior to DAS	Tool used in diagnosis of PAH	Accompanying PE	Treatment of PAH	Outcome of PAH
Minami *et al*, 2017 [8]	5	Median age: 60 (53–69) 2F/3M	CML	3–28	NR	1st, 2nd, and 3rd	IFN-α, IM and NIL	TTE	Not known	NR	NR
Ozgur Yurttas *et al*, 2015 [50]	5	Median age: 52 (34–66) 4F/1M	CML	2–25	100–140	2nd	HU, IFN-α, IM	3 ➔ TTE 2 ➔ RHC	2 ➔ No 3 ➔ Yes	2 ➔ DAS dose reduction 3➔ DAS cessation	Reversible
Weatherald *et al*, 2017 [72]	21	Median age: 52 15F/6M	19 ➔ CML 1➔ Ph + ALL 1➔ systemic mastocytosis	8–74	NR	1st, 2nd and 3rd	HU, IFN-α, Ara-C	21 ➔ RHC	2 ➔ No 19 ➔ Yes	10 ➔ DAS cessation 11➔ DAS cessation + PDE inhibitors	14 ➔ Reversible 7 ➔ Irreversible

ADR, adriamycin; allo-HSCT, allogeneic haematopoietic stem cell transplantation; Ara-C, cytosine arabinoside; BOS, bosentan; CML, chronic myeloid leukaemia; DAS, dasatinib; DAU, daunorubicin; F, female; FLAG Ida, fludarabine, ARA-C, G-CSF, idarubicin; G-CSF, granulocyte colony-stimulating factor; HU, hydroxyurea; hyper CVAD, hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone; IFN-α, interferon-alpha; IM, imatinib; L-asp, L-asparaginase; M, male; 6-MP, 6-mercaptopurine; MTX, methotrexate; NA, not available; NR, not reported; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; PE, pleural effusion; peg IFN-α, pegylated interferon-alpha; Ph + ALL, Philadelphia-positive acute lymphoblastic leukaemia; PRED, prednisone; RHC, right heart catheterization; SIL, sildenafil; TTE, transthoracic echocardiography; VCR, vincristine

[a]Studies published in languages other than English were excluded

(Table 2). Whether the possibility of PAH changes with the choice of dasatinib as the first- or late-line treatment strategy is not clear, and remains to be investigated.

The clear association of dasatinib use with PAH, and its resolution on discontinuation of the drug suggest a causal role for this agent in the development of the condition. The occurrence of late-onset PAH in CML patients suggests a chronic pathological mechanism with an insidious onset, rather than an acute inflammatory or cardiac aetiology, but the pathogenesis remains to be elucidated. Moreover, unlike the defined risk factors in PE related to dasatinib use (e.g. older age, high dose of the drug, use of the drug twice per day, long-term use, comorbidities), no risk factors or predictive factors have been identified yet. Shah *et al*. [55] searched the Bristol-Myers Squibb database for cases of dasatinib-induced PAH occurring between 28 June 2006 (the date of the first regulatory approval of dasatinib) and 31 October 2013. The authors identified the largest series reported to date, comprising 41 cases of RHC-confirmed PAH, including 22 unpublished and 19 previously reported cases. In their study, 68% of the cases had concomitant PE, whereas 82% of those with medical history available had cardiovascular or pulmonary risk factors/symptoms in their medical history at the time of presentation with PAH. However, the authors could not identify any specific attributes as being associated with a greater risk of developing PAH while receiving dasatinib (including concomitant PE); however, because of the limited number of reported events, formal statistical analyses could not be performed [55].

PAH has a multifactorial pathophysiology, including vasoconstriction, remodelling of the pulmonary vessel wall (resulting from vascular smooth muscle and endothelial cell proliferation) and thrombosis, which all contribute to increased pulmonary vascular resistance. PDGFR signalling-related cellular proliferation has been suggested as an important contributor to the development and progression of PAH [2–4, 34, 49, 52, 54, 56]. The ability to inhibit PDGFR signalling suggests similar effects of imatinib and dasatinib on pulmonary vascular remodelling. However, while imatinib was thought to be effective in the treatment of PAH in several cases and in a study, it appears that, surprisingly, dasatinib is associated with the onset of PAH [55–62]. These different behaviours of the two TKIs seem to be caused by the fact that dasatinib displays broader target tyrosine kinase profiles than imatinib and nilotinib [36]. The main known difference between dasatinib and other TKIs seems to be the additional inhibition of Src family kinases. These kinases are thought to be involved in the development of reversible exudative PE related to dasatinib use [37, 38]. In addition, it is speculated that Src inhibition may also play a role in the development of dasatinib-induced PAH, by means of a similar mechanism [55]. Src tyrosine kinase is expressed abundantly in vascular tissue, and activation of Src appears to play a crucial role in smooth muscle cell proliferation and vasoconstriction. The inhibition of Src family kinases, which degrade activated PDGFR, can increase signalling by PDGF and other growth factors. An additional explanation may be related to off-target kinase inhibition [2, 4, 52, 57, 63–66]. Recently, Guignabert and coworkers [67] published an article in which the possible mechanisms of dasatinib-induced PAH was discussed. The authors demonstrated that chronic dasatinib therapy may cause pulmonary endothelial damage in humans and rodents, and they suggested that treatment with this drug attenuates hypoxic pulmonary vasoconstriction responses and increases susceptibility to experimental PAH in rats, unlike in rats treated with imatinib [67]. In contrast to other studies, the authors suggested that dasatinib mediated endothelial cell dysfunction via increased production of reactive oxidants that was independent of Src family kinases. Although these findings may help us to understand the pathophysiology of this condition, further studies are still needed to reveal the precise mechanism of dasatinib-induced PAH.

PAH seems to be reversible with cessation of the drug, although complete resolution may not be detected, and PAH-specific therapy may need to be started. Together with discontinuation of dasatinib and PAH-specific treatment strategies, clinical and biochemical improvements have been observed in most of the cases in the literature [2, 4, 34, 42, 43, 49–52, 54, 55, 57, 68–71]. However, very recently Weatherald *et al*. [72] discussed the long-term outcomes of dasatinib-induced PH in 21 incident, RHC-confirmed cases from the French Pulmonary Hypertension Registry, and revealed that patients treated with PAH medications had worse baseline haemodynamics but similar long-term outcomes to untreated ones. In this study, they also found that dasatinib-induced PAH frequently improved after discontinuation but persisted in over one-third of patients [72]. Moreover, especially in these persisting patients, PAH-specific treatment modalities could be beneficial.

A proposed algorithm for the management of dasatinib-induced PAH is summarized in Figure 1. When dasatinib-related PAH is suspected on the basis of symptoms, non-invasive tests, including chest X-ray and TTE, should be performed. If the suspicion still persists, then RHC can be carried out to obtain a precise diagnosis. As soon as dasatinib-related PAH is diagnosed, dasatinib treatment should be stopped, and whenever the subsequent improvement is thought to be inadequate, it would be reasonable to add a PAH-specific agent.

As pulmonary vascular toxicity related to dasatinib is thought to be molecule- rather than class related, it seems reasonable to switch to another TKI after cessation of dasatinib for the treatment of CML and Ph + ALL [3, 4, 35, 52, 73]. For example, in most of the cases with CML/ALL in the literature, nilotinib treatment was initiated after stopping dasatinib, and PAH did not reoccur [2, 4, 34, 49, 51, 57, 68–71]. Minami and colleagues [8] published a case series describing patients with PAH in relation to their use of TKIs. These authors screened 105 patients with CML-CP who had been exposed to imatinib, dasatinib or nilotinib for PAH with TTE, and found that five of the 38 patients receiving dasatinib had an elevated mean tricuspid regurgitation peak gradient (mTRPG) suggestive of PAH, of whom only one had symptoms of dyspnoea [8]. Interestingly, in their study, besides dasatinib, three patients receiving nilotinib and one patient taking imatinib were also found to have an elevated mTRPG on TTE screening. However, it should be noted that in the study by Minami and coworkers, the diagnosis of PAH was not confirmed with RHC (although it is not always necessary to do so) [8]. High right ventricular systolic pressure detected on TTE can also be secondary to anaemia, high cardiac output

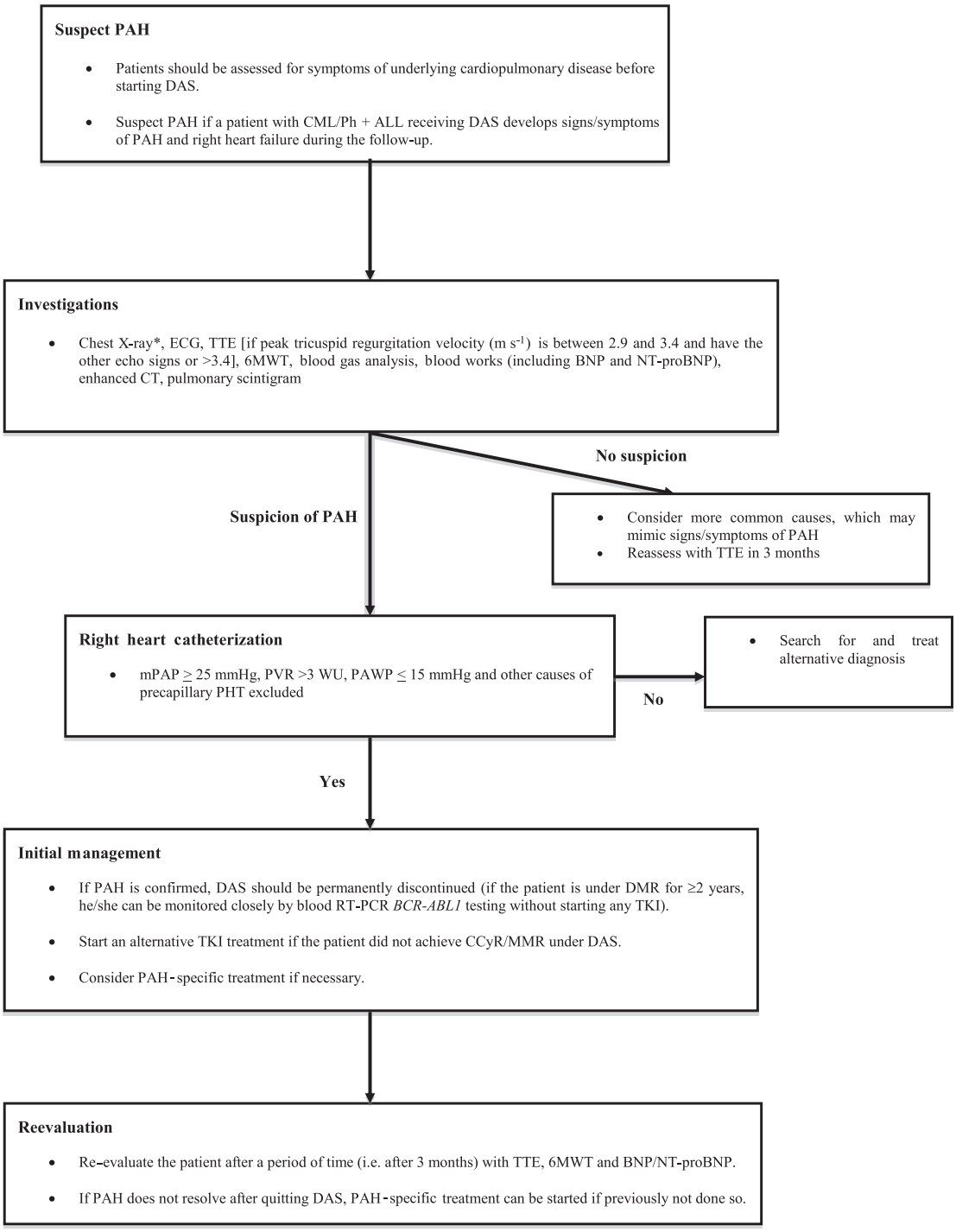

Figure 1

Management of dasatinib-induced pulmonary arterial hypertension. 6MWT, 6-min walking test; *BCR-ABL1*, fusion of the breakpoint cluster region (*BCR*) and the Abelson murine leukaemia (*ABL1*) genes; BNP, brain natriuretic peptide; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CT, computed tomography; DAS, dasatinib; DMR, deep molecular response; ECG, electrocardiography; MMR, major molecular response; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; Ph + ALL, Philadelphia-positive acute lymphoblastic leukaemia; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RT-PCR, real-time polymerase chain reaction; TKI, tyrosine kinase inhibitor; TTE, transthoracic echocardiography; WU, Wood units

*As pleural effusion is much more common than PAH, a chest X-ray should be performed initially

and postcapillary PH. Although imatinib has been considered effective in the treatment of PAH in some studies, as mentioned above [55–62], the Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES) study [74] and the recently published long-term data of Frost *et al*. [75] suggested that imatinib may not be useful in the treatment of PAH, showing an unacceptably high rate of AEs. In addition to this, Zakrzewski *et al*. [76] presented the first case report of PAH confirmed only with TTE in a patient treated with nilotinib for CML, and found that pulmonary pressure decreased after discontinuation of the drug. Moreover, Ustun and colleagues [77] recently presented a case of recurrent PE after the use of both dasatinib and nilotinib. These authors discuss the dilemma about whether the PE was related to the delayed recurrence of the dasatinib-induced effect, even though, the drug was discontinued, or to a rare AE of nilotinib that started after dasatinib cessation. More recently, Quilot *et al*. [78] published a study describing a CML patient who developed PAH under ponatinib therapy which improved with cessation of the drug and PAH-targeted therapy. In addition, Riou *et al*. [79] presented two cases in which bosutinib was used following dasatinib therapy. These patients had a history of dasatinib-induced PAH, and following the initiation of bosutinib treatment the PAH deteriorated. However, the authors pointed out that potentiation or a facilitation effect of dasatinib in these cases could not be excluded. As dasatinib, ponatinib and bosutinib all inhibit Src tyrosine kinase, this case also supports the hypothesis that the Src tyrosine kinase pathway may be implicated in dasatinib-induced PAH. Combining these studies, it is clear that the possible class effect of other TKIs in the generation of PAH should also be studied further.

Current status and future directions

At present, therapy with TKIs is generally considered lifelong, and information on long-term AEs is worthwhile. Therefore, it is reasonable to screen routinely for PAH by TTE before commencing dasatinib treatment, especially in patients with underlying cardiopulmonary disease. In addition, it is advisable to perform additional diagnostic testing in patients who are to receive this therapy who develop dyspnoea or other symptoms suggestive of PAH, independently both of the dosing regimen of the drug and of the concomitant occurrence of PE. When these investigations indicate possible PAH, an RHC is essential, to confirm the diagnosis.

Although it is an efficacious drug, dasatinib can be associated with some AEs, including PAH, especially when administered for longer periods. The incidence and the underlying molecular mechanisms of dasatinib-induced PAH should be elucidated in future studies.

Although most of the reported cases with dasatinib-induced PAH have had some degree of clinical and biochemical improvements after cessation of drug treatment, in some patients PAH-specific therapies can be needed. Following cessation of the causative agent, patients should be monitored closely, and if progression of PAH is observed, PAH-specific treatment strategies should be started promptly. It may also be reasonable to recommend starting dasatinib-induced PAH therapy at the same time as cessation of the drug in some cases. Dasatinib should not be rechallenged in patients with dasatinib-induced PAH, and alternative TKIs should be chosen. Alternatively, in CML patients who develop PAH during dasatinib therapy with a deep molecular response (MR^4 or $MR^{4.5}$) for ≥2 years, TKI therapy can be discontinued, with close monitoring of *BCR-ABL1* blood levels by real-time polymerase chain reaction testing, without starting on a TKI.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [80], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [81].

Competing Interests

N.Ö.Y. has no conflict of interest to declare. A.E.E. has received honoraria for advisory board membership from Novartis, and has received lecture fees from Novartis and Bristol-Myers Squibb.

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References

1 Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, *et al*. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013; 62: D42–50.

2 Rasheed W, Flaim B, Seymour JF. Reversible severe pulmonary hypertension secondary to dasatinib in a patient with chronic myeloid leukemia. Leuk Res 2009; 33: 861–4.

3 Montani D, Seferian A, Savale L, Simonneau G, Humbert M. Drug-induced pulmonary arterial hypertension: a recent outbreak. Eur Respir Rev 2013; 22: 244–50.

4 Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, *et al*. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012; 125: 2128–37.

5 Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, *et al*. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The task force on diagnosis and treatment of pulmonary arterial hypertension of the European Society of Cardiology. Eur Heart J 2004; 25: 2243–78.

6 Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, *et al*. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016; 37: 67–119.

7 Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 233–71.

8 Minami M, Arita T, Iwasaki H, Muta T, Aoki T, Aoki K, *et al*. Comparative analysis of pulmonary hypertension in patients treated with imatinib, nilotinib and dasatinib. Br J Haematol 2017; 177: 578–87.

9 Warwick G, Thomas PS, Yates DH. Biomarkers in pulmonary hypertension. Eur Respir J 2008; 32: 503–12.

10 Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, *et al*. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62: D34–41.

11 Garypidou V, Vakalopoulou S, Dimitriadis D, Tziomalos K, Sfikas G, Perifanis V. Incidence of pulmonary hypertension in patients with chronic myeloproliferative disorders. Haematologica 2004; 89: 245–6.

12 Guilpain P, Montani D, Damaj G, Achouh L, Lefrère F, Le Pavec J, *et al*. Pulmonary hypertension associated with myeloproliferative disorders: a retrospective study of ten cases. Respiration 2008; 76: 295–302.

13 Di Stefano F. Pulmonary arterial hypertension and chronic myeloproliferative disorders. Am J Respir Crit Care Med 2006; 174: 616.

14 Adir Y, Humbert M. Pulmonary hypertension in patients with chronic myeloproliferative disorders. Eur Respir J 2010; 35: 1396–406.

15 Adir Y, Elia D, Harari S. Pulmonary hypertension in patients with chronic myeloproliferative disorders. Eur Respir J 2015; 24: 400–10.

16 Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009; 53: 1119–26.

17 Alexopoulos D, Lazzam C, Borrico S, Fiedler L, Ambrose JA. Isolated chronic mitral regurgitation with preserved systolic left ventricular function and severe pulmonary hypertension. J Am Coll Cardiol 1989; 14: 319–22.

18 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992; 327: 76–81.

19 Ghofrani HA, Galie N, Grimminger F, Grunig E, Humbert M, Jing ZC, *et al*. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013; 369: 330–40.

20 Barst RJ, McGoon M, McLaughlin VV, Tapson V, Rich S, Rubin L, *et al*. Beraprost therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2003; 41: 2119–25.

21 Simonneau G, Torbicki A, Hoeper MM, Delcroix M, Karlocai K, Galie N, *et al*. Selexipag, an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J 2012; 40: 874–80.

22 Hyduk A, Croft JB, Ayala C, Zheng K, Zheng ZJ, Mensah GA. Pulmonary hypertension surveillance – United States, 1980–2002. MMWR Surveill Summ 2005; 54: 1.

23 Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012; 142: 448–56.

24 Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. Science 1990; 247: 824–30.

25 Heisterkamp N, Groffen J, Stephenson JR, Spurr NK, Goodfellow PN, Solomon E, *et al*. Chromosomal localization of human cellular homologues of two viral oncogenes. Nature 1982; 299: 747–9.

26 Abruzzese E, Breccia M, Latagliata R. Second-generation tyrosine kinase inhibitors in first-line treatment of chronic myeloid leukaemia (CML). BioDrugs 2014; 28: 325.

27 Keskin D, Eskazan AE. The treatment of chronic myeloid leukaemia (CML) in the era of tyrosine kinase inhibitors – what is new in the battle of CML? Eur Oncol Haematol 2015; 11: 30–1.

28 Rogers G, Hoyle M, Thompson Coon J, Moxham T, Liu Z, Pitt M, *et al*. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012; 16: 1–410.

29 Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, *et al*. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010; 362: 2260–70.

30 Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, *et al*. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010; 362: 2251–9.

31 Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, *et al*. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013; 122: 872–84.

32 McCormack PL, Keam SJ. Dasatinib: a review of its use in the treatment of chronic myeloid leukaemia and Philadelphia chromosome-positive acute lymphoblastic leukaemia. Drugs 2011; 71: 1771–95.

33 Keskin D, Sadri S, Eskazan AE. Dasatinib for the treatment of chronic myeloid leukemia: patient selection and special considerations. Drug Des Devel Ther 2016; 10: 3355–61.

34 Orlandi EM, Rocaa B, Pazzano AS, Ghio S. Reversible pulmonary arterial hypertension likely related to long-term, low-dose dasatinib treatment for chronic myeloid leukaemia. Leuk Res 2012; 36: e4–6.

35 Godinas L, Guignabert C, Seferian A, Perros F, Bergot E, Sibille Y, *et al*. Tyrosine kinase inhibitors in pulmonary arterial hypertension: a double-edge sword? Semin Respir Crit Care Med 2013; 34: 714–24.

36 Swords R, Mahalingam D, Padmanabham S, Carew J, Giles F. Nilotinib: optimal therapy for patients with chronic myeloid leukemia and resistance or intolerance to imatinib. Drug Des Devel Ther 2009; 3: 89–101.

37 Quintas-Cardama A, Kantarjian H, O'Brien S, Borthakur G, Bruzzi J, Munden R, *et al*. Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. J Clin Oncol 2007; 25: 3908–14.

38 Shah NP, Kantarjian HM, Kim DW, Rousselot P, Llacer PE, Enrico A, *et al*. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. Haematologica 2010; 95: 232–40.

39 Porkka K, Khoury HJ, Paquette RL, Matloub Y, Sinha R, Cortes JE. Dasatinib 100 mg once daily minimizes the occurrence of pleural effusion in patients with chronic myeloid leukemia in chronic phase and efficacy is unaffected in patients who develop pleural effusion. Cancer 2010; 116: 377–86.

40 Eskazan AE, Soysal T, Ongoren S, Gulturk E, Ferhanoglu B, Aydin Y. Pleural and pericardial effusions in chronic myeloid leukemia patients receiving low-dose dasatinib therapy. Haematologica 2011; 96: e15.

41 Eskazan AE, Eyice D, Kurt EA, Elverdi T, Yalniz FF, Salihoglu A, *et al*. Chronic myeloid leukemia patients who develop grade I/II pleural effusion under second-line dasatinib have better responses and outcomes than patients without pleural effusion. Leuk Res 2014; 38: 781–7.

42 Mattei D, Feola M, Orzan F, Mordini N, Rapezzi D, Gallamini A. Reversible dasatinib-induced pulmonary arterial hypertension and right ventricle failure in a previously allografted CML patient. Bone Marrow Transplant 2009; 43: 967–8.

43 Hennings JK, Keller G, Baumann HJ, Honecker F, Kluge S, Bokemeyer C, *et al*. Multi tyrosine kinase inhibitor dasatinib as novel cause of severe pre-capillary pulmonary hypertension? BMC Pulm Med 2011; 11: 30.

44 Gurtner HP. Chronic pulmonary hypertension of vascular aetiology, plexogenic pulmonary arteriopathy and the appetite depressant Aminorex: lessons from an epidemic. Schweiz Med Wochenschr 1985; 115: 818–27.

45 Gurtner HP. Aminorex and pulmonary hypertension: a review. Cor Vasa 1985; 27: 160–71.

46 Eddahibi S, Adnot S. Anorexigen-induced pulmonary hypertension and the serotonin (5-HT) hypothesis: lessons for the future in pathogenesis. Respir Res 2002; 3: 9.

47 Loogen F, Worth H, Schwan G, Goeckenjan G, Lösse B, Horstkotte D. Long-term follow-up of pulmonary hypertension in patients with and without anorectic drug intake. Cor Vasa 1985; 27: 111–24.

48 FDA Drug Safety Communication: Sprycel (dasatinib) and risk of pulmonary arterial hypertension (10-11-2011). https://www.fda.gov/Drugs/DrugSafety/ucm275155.htm (last accessed 20 February 2018)

49 Sano M, Saotome M, Urushida T, Katoh H, Satoh H, Ohnishi K, *et al*. Pulmonary arterial hypertension caused by treatment with dasatinib for chronic myeloid leukemia – critical alert. Intern Med 2012; 51: 2337–40.

50 Ozgur Yurttas N, Sadri S, Keskin D, Berk S, Oztunali Erdogan I, Yalniz FF, *et al*. Real-life data and a single center experience on dasatinib-induced pulmonary arterial hypertension in patients with Philadelphia chromosome-positive leukemias. Blood 2015; 126: 4037.

51 Wang HC, Lee CS, Liu TC. Reversible dasatinib-related pulmonary arterial hypertension diagnosed by noninvasive echocardiography. Kaohsiung J Med Sci 2015; 31: 165–6.

52 Kim JC, Shin SH, Yi HG, Kim SH, Woo SI, Kim DH, *et al*. Rapid-onset pulmonary arterial hypertension in a patient with acute lymphoblastic leukemia treated with dasatinib. Herz 2013; 38: 931–3.

53 Morishita S, Hagihara M, Itabashi M, Ishii Y, Yamamoto W, Numata A, *et al*. Development of pulmonary arterial hypertension during oral dasatinib therapy for chronic myelogenous leukemia. Rinsho Ketsueki 2016; 57: 999–1003.

54 Taçoy G, Çengel A, Özkurt ZN, Türkoğlu S. Dasatinib-induced pulmonary hypertension in acute lymphoblastic leukemia: case report. Arch Turk Soc Cardiol 2015; 43: 78–81.

55 Shah NP, Wallis N, Farber HW, Mauro MJ, Wolf RA, Mattei D, *et al*. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. Am J Hematol 2015; 90: 1060–4.

56 Puri A, McGoon MD, Kushwaha SS. Pulmonary arterial hypertension: a current therapeutic strategies. Nat Clin Pract Cardiovasc Med 2007; 4: 319–29.

57 Dumitrescu D, Seck C, ten Freyhaus H, Gerhardt F, Erdmann E, Rosenkranz S. Fully reversible pulmonary arterial hypertension associated with dasatinib treatment for chronic myeloid leukaemia. Eur Respir J 2011; 38: 218–20.

58 Ghofrani HA, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. N Engl J Med 2005; 353: 1412–3.

59 Patterson KC, Weissmann A, Ahmadi T, Farber HW. Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. Ann Intern Med 2006; 145: 152–3.

60 Souza R, Sitbon O, Parent G, Simonneau G, Humbert M. Long term imatinib treatment in pulmonary arterial hypertension. Thorax 2006; 61: 736.

61 ten Freyhaus H, Dumitrescu D, Bovenschulte H, Erdmann E, Rosenkranz S. Significant improvement of right ventricular function by imatinib mesylate in scleroderma-associated pulmonary arterial hypertension. Clin Res Cardiol 2009; 98: 265–7.

62 Ghofrani HA, Morrell NW, Hoeper MM, Olschewski H, Peacock AJ, Barst RJ, *et al*. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. Am J Respir Crit Care Med 2010; 182: 1171–7.

63 Rosenkranz S, Ikuno Y, Leong FL, Klinghoffer RA, Miyake S, Band H, *et al*. Src family kinases negatively regulate platelet-derived growth factor a receptor-dependent signaling and disease progression. J Biol Chem 2000; 275: 9620–7.

64 Oda Y, Renaux B, Bjorge J, Saifeddine M, Fujita DJ, Hollenberg MD. Csrc is a major cytosolic tyrosine kinase in vascular tissue. Can J Physiol Pharmacol 1999; 77: 606–17.

65 Olschewski H, Nagaraj C, Tang B, Balint Z, Hrzenjak A, Stacher E, *et al*. Novel role of Src family tyrosine kinase (srctk) in response of potassium channels in human pulmonary artery smooth muscle cells to hypoxia. Am J Respir Crit Care Med 2011; 183: A5484.

66 Pullamsetti SS, Berghausen EM, Dabral S, Tretyn A, Butrous E, Savai R, *et al*. Role of Src tyrosine kinases in experimental pulmonary hypertension. Arterioscler Thromb Vasc Biol 2012; 32: 1354–65.

67 Guignabert C, Phan C, Seferian A, Huertas A, Tu L, Thuillet R, *et al*. Dasatinib induces lung vascular toxicity and predisposes to pulmonary hypertension. J Clin Invest 2016; 126: 3207–18.

68 Groeneveldt JA, Gans SJ, Bogaard HJ, Vonk-Noordegraaf A. Dasatinib-induced pulmonary arterial hypertension unresponsive to PDE-5 inhibition. Eur Respir J 2013; 42: 869–70.

69 Yun S, Anwer F, Vincelette ND. Dasatinib-induced pulmonary hypertension in chronic myelogenous leukaemia. BMJ Case Rep 2014; 2014: pii: bcr2014204477.

70 Hong JH, Lee SE, Choi SY, Kim SH, Jang EJ, Bang JH, *et al*. Reversible pulmonary arterial hypertension associated with dasatinib for chronic myeloid leukemia. Cancer Res Treat 2015; 47: 937–42.

71 Buchelli Ramirez HL, Álvarez CM, Rodríguez Reguero JJ, García Clemente MM, Casan Clarà P. Reversible pre-capillary pulmonary hypertension due to dasatinib. Respir Care 2014; 59: e77–80.

72 Weatherald J, Chaumais MC, Savale L, Jaïs X, Seferian A, Canuet M, *et al*. Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. Eur Respir J 2017; 50: pii: 1700217.

73 Sprycel® (dasatinib). Full prescribing information. Princeton, NJ: Bristol-Myers Squibb, 2014.

74 Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, *et al*. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation 2013; 127: 1128–38.

75 Frost AE, Barst RJ, Hoeper MM, Chang HJ, Frantz RP, Fukumoto Y, *et al*. Long-term safety and efficacy of imatinib in pulmonary arterial hypertension. J Heart Lung Transplant 2015; 34: 1366–75.

76 Zakrzewski D, Seferynska I, Warzocha K, Hryniewiecki T. Elevation of pulmonary artery pressure as a complication of nilotinib therapy for chronic myeloid leukemia. Int J Hematol 2012; 96: 132–5.

77 Ustun C, Randall N, Podgaetz E, Amin K, Dincer HE. Severe dyspnoea in a patient with chronic myelogenous leukaemia on a tyrosine kinase inhibitor. Thorax 2015; 70: 701–4.

78 Quilot FM, Georges M, Favrolt N, Beltramo G, Foignot C, Grandvuillemin A, *et al*. Pulmonary hypertension associated with ponatinib therapy. Eur Respir J 2016; 47: 676–9.

79 Riou M, Seferian A, Savale L, Chaumais MC, Guignabert C, Canuet M, *et al*. Deterioration of pulmonary hypertension and pleural effusion with bosutinib following dasatinib lung toxicity. Eur Respir J 2016; 48: 1517–9.

80 Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucl Acid Res 2018; 46: D1091–106.

81 Alexander SPH, Fabbro D, Kelly E, Marrion NV, Peters JA, Faccenda E, *et al*. The Concise Guide to PHARMACOLOGY 2017/18: Enzymes. Br J Pharmacol 2017; 174: S272–359.