LETTERS

Fully reversible pulmonary arterial hypertension associated with dasatinib treatment for chronic myeloid leukaemia

To the Editors:

Pulmonary arterial hypertension (PAH) is a devastating disease that is characterised by a progressive increase in pulmonary vascular resistance (PVR), chronic right heart failure and premature death. Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure ($\bar{P}$pa) $\geqslant$25 mmHg at rest, and the haemodynamic definition discerns pre- and post-capillary PH [1]. Furthermore, PAH is distinguished from other forms of PH that may occur secondary to various underlying causes, including left heart disease, chronic lung disorders and thromboembolic disease [1]. Although the development of targeted PAH therapies, such as endothelin receptor antagonists, phosphodiesterase type-5 inhibitors (PDE5i) and prostanoids, has markedly improved the clinical situation and outcome of affected patients, the current medical treatment of PAH is not satisfactory.

Recently, tyrosine kinase inhibitors (TKIs), particularly imatinib, have been proposed as a potential novel treatment option in PAH [2–7]. Imatinib was the first TKI that achieved regulatory approval for the treatment of chronic myeloid leukaemia (CML) and has become the standard of care for patients with this disease, as it inhibits the hybrid *BCR–ABL* oncogene that is pathogenic in the development of CML. Imatinib inhibits several tyrosine kinases, including BCR–ABL, the platelet-derived growth factor receptor (PDGFR) and c-Kit. More recently, additional TKIs, including dasatinib and nilotinib, have been introduced for the treatment of CML in patients who are intolerant or unresponsive to imatinib.

The potential efficacy of imatinib in PAH is attributable to its inhibitory effect on the PDGFR. Platelet-derived growth factor (PDGF) is thought to play a pivotal role in the pathobiology of PAH by initiating and maintaining the underlying pulmonary vascular remodelling [7, 8]. Consistent with this, inhibition of PDGFR signalling by imatinib was recently shown to reverse PAH in animal models, and to improve the clinical situation in patients with severe PAH and inadequate response to established therapy [2–7]. Herein, we report the development of severe PAH associated with dasatinib treatment for CML, which completely resolved after termination of this TKI.

A 47-yr-old male presented with a 3-month history of progressive exertional dyspnoea (World Health Organization (WHO) functional class III), fatigue and dizziness. He was known to suffer from a Philadelphia chromosome-positive CML with b3a2 and b2a2 BCR–ABL transcripts. The patient did not have any other significant diseases. In particular, there were no known cardiac or respiratory conditions. At the time of presentation, CML had been medically treated for 7 yrs by the use of various compounds. The initial treatment consisted of a combination of PEGylated interferon-α and imatinib. This regimen had to be discontinued after 1 yr because of a significant liver enzyme elevation and recurrent exanthema. A rechallenge had produced the same side-effects. At that point, CML treatment was switched to dasatinib (70 mg·day^{-1} *b.i.d.*), with several dose adjustments over time because of recurrent pleural effusions that were first documented 13 months after initiation of dasatinib. At the time of presentation, the patient had been on a stable dasatinib dose of 100 mg·day^{-1} for 39 months.

On admission, physical examination revealed a systolic heart murmur, a resting tachycardia (heart rate 100 beats·min^{-1}) with normal blood pressure (120/85 mmHg), jugular venous distention, hepatomegaly and peripheral oedema. Electrocardiography showed right axis deviation, a right bundle branch block and T-wave inversions in leads V1–4. The patient had grade 3 bilateral pleural effusions requiring thoracentesis and pleural fluid analysis was consistent with an exudate. Transthoracic echocardiography revealed regularly sized left heart chambers and left ventricular ejection fraction (LVEF) was normal. However, right heart cavities were enlarged (right atrial area 22 cm^2; basal right ventricular end-diastolic diameter 51 mm) and a mild pericardial effusion was detected. The systolic pulmonary artery pressure (Ppa) was estimated at 61 mmHg and right ventricular function was impaired, as assessed by a reduced tricuspid annular plane systolic excursion of 16 mm. The patient was subjected to right heart catheterisation, which demonstrated severe pre-capillary PH. There was a marked elevation of the $\bar{P}$pa to 60 mmHg, pulmonary capillary wedge pressure was normal (11 mmHg), and cardiac output (CO) was reduced to 3.6 L·min^{-1}. Consequently, the calculated PVR was elevated at 13.6 Wood units. The patient was unresponsive to vasoreactivity testing with inhaled iloprost.

Potential other causes of PH, such as pulmonary embolism or parenchymal lung disease, were ruled out by contrast-enhanced spiral computed tomography and a ventilation/perfusion scan. Consistent with signs of right ventricular strain, laboratory testing showed significantly elevated N-terminal pro-brain natriuretic peptide serum levels (2,888 ng·L^{-1}) and the 6-min walk distance was limited to 435 m. Furthermore, laboratory screening tests for HIV and for systemic rheumatic diseases, including antinuclear antibodies,

antibodies to double-stranded DNA and anti-Scl-70 antibodies were negative. Concurrent administration of drugs or toxins suspected to play a predisposing or facilitating role in the development of PAH was ruled out. Due to previously reported clues for dasatinib-related development of PAH [9–11], CML treatment with dasatinib was permanently discontinued and a targeted PAH therapy with the PDE5i sildenafil was initiated. Subsequently, the patient underwent close follow-up investigations.

Re-evaluation after 2 months revealed a significant improvement of the clinical condition to WHO functional class II and right heart catheterisation evidenced a marked decrease in P_{pa}, accompanied by a substantial increase in CO and a related decrease in PVR. Since the patient's leukaemia required further treatment, the alternate TKI nilotinib was started at a dose of 400 mg $b.i.d.$ Subsequently, repeat noninvasive evaluations showed normalisation of all measured parameters, such that targeted PAH therapy with sildenafil was stopped after 6 months. A third right-heart catheterisation was performed 2 weeks later, and confirmed a $\bar{P}_{pa}$ below the threshold for PH and even for borderline PH [1, 12]. The other haemodynamic parameters had improved accordingly. This coincided with complete resolution of breathlessness. To date, 3 months after discontinuation of specific PAH therapy, the patient has remained asymptomatic with no evidence of recurrent PAH or pleural effusions and was continued on nilotinib with close monitoring. The details of the invasive and noninvasive diagnostic work-up for this patient are shown in table 1.

The case we present here is consistent with recent reports on transient PAH in conjunction with pleural effusion secondary to

the TKI dasatinib that have been described in a few patients [9–11]. In all cases, dasatinib had been given for a rather long period of time (18–60 months) before PAH developed and all patients presented with pleural effusions. Notably, these patients also demonstrated a rapid onset of symptoms and reversal of pulmonary vasculopathy after termination of dasatinib, leading to haemodynamic normalisation (table 2). This is remarkable because complete remission and normalisation of pulmonary hemodynamics is usually not achieved in PAH by medical treatment. In the present case, pulmonary haemodynamics had normalised 6 months after the onset of PAH, even after termination of PAH therapy. Therefore, it is assumed that the pathophysiological mechanism leading to increased PVR and PAH differed from the vascular alterations typically seen in PAH.

The ability to inhibit PDGFR signalling suggests similar effects of imatinib and dasatinib on pulmonary vascular remodelling. However, while imatinib was effective for the treatment of PAH in several cases and a recent phase II study [3–7], it appears that dasatinib is surprisingly associated with the

TABLE 1	Invasive and noninvasive evaluation during the course of the disease: display of key parameters					
	Baseline	Time months				
		1	2	4	6	9
Systolic P_{pa} mmHg	82		45		39	
Diastolic P_{pa} mmHg	44		17		11	
$\bar{P}_{pa}$ mmHg	60		28		20	
P_{pcw} mmHg	11		7		7	
$\bar{P}_{ra}$ mmHg	20		4		3	
CO L·min^{-1}	3.6		4.8		6.3	
PVR Wood units	13.6		4.4		2.0	
NT-proBNP ng·L^{-1}	2888	1.037	282	72	50	25
6MWD m	435	550	600	600	600	600
RVEDD mm	51	44	47	38	35	35
TAPSE mm	16	17	18	22	21	25

P_{pa}: pulmonary artery pressure; $\bar{P}_{pa}$: mean P_{pa}; P_{pcw}: pulmonary capillary wedge pressure; $\bar{P}_{ra}$: mean right atrial pressure; CO: cardiac output; PVR: pulmonary vascular resistance; NT-proBNP: N-terminal pro-brain natriuretic peptide; 6MWD: 6-min walk distance; RVEDD: right ventricle end-diastolic diameter; TAPSE: tricuspid annular plane systolic excursion.

TABLE 2	Comparison of haemodynamic evolution in the case reports previously described in the literature and the presented case				
	Baseline	Time months			
		2	3	6	10
Systolic P_{pa} mmHg					
Rasheed [10]	70+P_{ra}#	31+P_{ra}#			
Mattei [11]	66		48		40
Present case	82	45		39	
Diastolic P_{pa} mmHg					
Rasheed [10]					
Mattei [11]	28		19		17
Present case	44	17		11	
$\bar{P}_{pa}$ mmHg					
Rasheed [10]					
Mattei [11]	40		29		25
Present case	60	28		20	
P_{pcw} mmHg					
Rasheed [10]					
Mattei [11]					
Present case	11	7		7	
CO L·min^{-1}					
Rasheed [10]					
Mattei [11]	3.9		6.47		7.23
Present case	3.6	4.8		6.3	
PVR Wood units					
Rasheed [10]					
Mattei [11]	8.2		7.23		2.3
Present case	13.6	4.4		2.0	

P_{pa}: pulmonary artery pressure; $\bar{P}_{pa}$: mean P_{pa}; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; PVR: pulmonary vascular resistance; P_{ra}: right atrial pressure. #: systolic P_{pa} estimated by echocardiography.

onset of PAH, at least in some patients. This raises questions about the underlying mechanism and the differences between dasatinib and other TKIs. Dasatinib is a multitarget kinase inhibitor of BCR–ABL, the PDGFR, Src, and c-Kit, which is structurally distinct from imatinib, has a broader spectrum of activity and ~300-fold greater potency than imatinib in *in vitro* studies. Global chemical proteomic profiling of imatinib, dasatinib and nilotinib identified novel kinase and nonkinase targets for the three TKIs with only a small overlap covering the ABL kinases [13]. Imatinib and nilotinib displayed much more specific target profiles compared with dasatinib, suggesting that dasatinib has a broad range of activity in multiple biological processes. The main known difference in the kinase profile between dasatinib and other TKIs, such as imatinib or nilotinib, is the additional inhibition of Src family kinases. It may therefore be speculated that Src inhibition may play a role in the development of dasatinib-associated PAH. It has recently been reported that dasatinib inhibits PDGF-induced proliferation and migration of vascular smooth muscle cells *via* inhibition of both PDGFR activity and PDGF-dependent Src activation downstream of the PDGFR [14], which may be beneficial in PAH. However, Src family kinases are required for degradation of activated PDGFRs [15]. Hence, inhibition of Src may result in increased signalling by PDGF and possibly other growth factors. An additional explanation may be related to off-target kinase inhibition. These mechanisms may affect pulmonary vascular wall integrity, possibly leading to (peri)-vascular oedema and subsequent PVR increase.

The clear association of pleural effusions and PAH with dasatinib intake and their resolution upon discontinuation of dasatinib suggest a causal role of the drug in disease development. Pleural effusions occur in 17–35% (grades 3–4 in 4%) of dasatinib-treated patients [9], but were not found in individuals treated with imatinib or nilotinib. An increase in P_{pa} was detected at the onset of pleural effusions in a subset of CML patients treated with dasatinib, suggesting the possibility of drug-related PAH [9–11]. A potential concern with TKIs, particularly imatinib, is cardiotoxicity, which is attributable to their inhibitory effect on c-Abl [16]. However, LVEF was normal in all reported cases of dasatinib-associated PAH, and the fact that most pleural effusions were exudates also argues against primary cardiac impairment but indicates an alternative pathological mechanism. The occurrence of PAH with pleural effusions at a late onset (26 months in our patient) suggests a chronic pathological mechanism with an insidious onset rather than an acute inflammatory or cardiac aetiology. Transient parenchymal changes in the lung have been described in patients on dasatinib therapy, all of which resolved after drug withdrawal [17].

In conclusion, chronic treatment with dasatinib may be complicated by severe, albeit reversible PAH and right ventricular failure that occur concurrent with pleural effusions. The incidence of dasatinib-associated PAH and the underlying molecular mechanisms should be elucidated in future studies.

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