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Bosutinib therapy resulting in severe deterioration of pre-existing pulmonary arterial hypertension

To the Editor:

We read with interest the recent correspondence from Quilot *et al.* [1] describing a likely case of ponatinib-associated pulmonary arterial hypertension (PAH). The authors hypothesised that the mechanism by which tyrosine kinase inhibitors (TKIs) such as dasatinib and ponatinib, used for the treatment of chronic myeloid leukaemia (CML), induce PAH may involve their common inhibition of the non-receptor tyrosine kinase, Src [1]. Here, we present a patient who developed marked worsening of pre-existing TKI-associated PAH following commencement of bosutinib, a third-generation TKI also known to inhibit Src [2]. After marked improvement on withdrawal of bosutinib, the patient experienced further significant worsening of PAH after commencing ponatinib. We believe this is the first reported case linking bosutinib with PAH. It also supports the association between ponatinib and PAH and represents the first time that the development or worsening of PAH associated with multiple TKIs in the same patient has been reported.

A 39-year-old man was diagnosed with CML in 2001. He had no other medical history of note. Following initial disease control with imatinib (March 2004–October 2009), he was switched to dasatinib because of loss of cytogenetic response. After 12 months of therapy, he became progressively breathless and developed pleural effusions. He was given diuretics and dasatinib was stopped in January 2011. Despite resolution of the pleural effusions and initial improvement in symptoms, he subsequently became more breathless and was assessed in our pulmonary hypertension (PH) unit in March 2011. Right heart catheterisation (RHC) confirmed severe PAH (mean right atrial pressure 15 mmHg; mean pulmonary arterial pressure 55 mmHg; pulmonary arterial wedge pressure 11 mmHg; cardiac index 2.5 $L \cdot min^{-1} \cdot m^{-2}$; pulmonary vascular resistance 17.6 Wood units; and mixed venous oxygen saturation 58%). Perfusion lung scanning excluded thromboembolic disease and there was no parenchymal lung disease or pleural effusions on computed tomography. His exercise capacity, as assessed by incremental shuttle walking distance (ISWD), was 180 m and he was in the World Health Organization (WHO) functional class (FC) III (figure 1). He was diagnosed with PAH associated with dasatinib therapy and commenced sildenafil 25 mg three times a day.

By May 2011, he had demonstrated a good response to sildenafil with ISWD increasing to 680 m and his performance status had improved to WHO FC II. He subsequently commenced nilotinib 400 mg twice a day in June 2011. In October 2011, he complained of some worsening of symptoms and sildenafil was increased to 50 mg three times a day. His symptoms stabilised for the next 9 months, but in July 2012 he

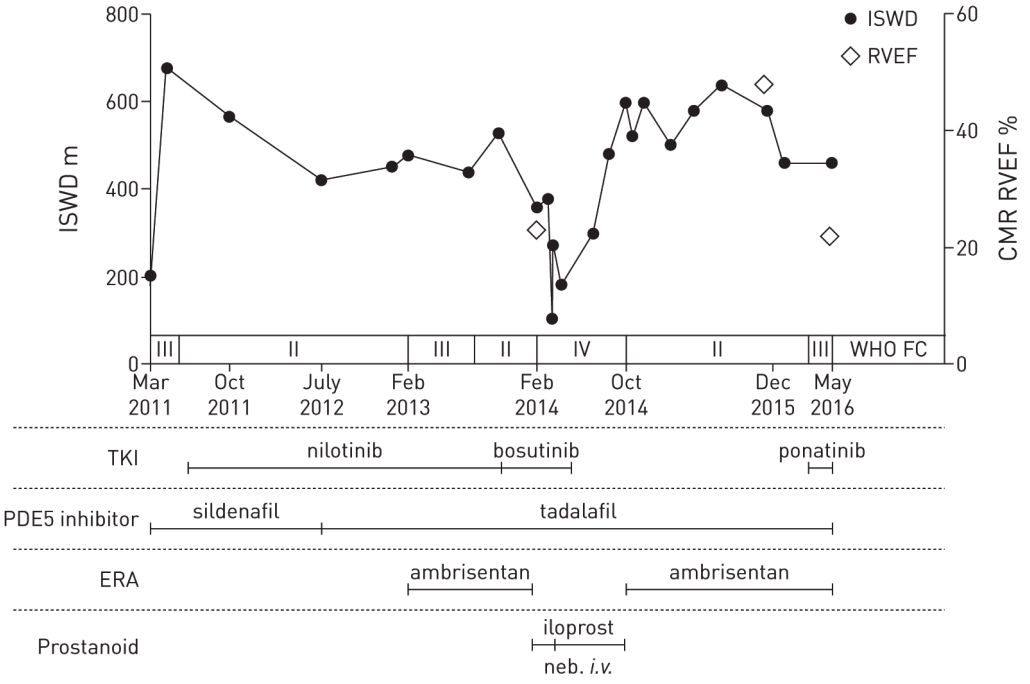

FIGURE 1 Exercise capacity, World Health Organization (WHO) functional class (FC), leukaemia therapy and pulmonary arterial hypertension therapy. ISWD: incremental shuttle walking distance; CMR: cardiac magnetic resonance; RVEF: right ventricular ejection fraction; TKI: tyrosine kinase inhibitor; PDE5: phosphodiesterase type 5; ERA: endothelin receptor antagonist; neb.: nebulised.

complained of further worsening of symptoms and sildenafil was changed to tadalafil 40 mg once a day in case compliance was an issue. By February 2013, he had deteriorated to WHO FC III and repeat RHC demonstrated a mean pulmonary arterial pressure 57 mmHg, cardiac index 2.4 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance 12.7 Wood units. Ambrisentan was added and by August 2013 he had symptomatically improved back to WHO FC II.

In December 2013, his CML treatment was switched to bosutinib 500 mg once a day because of loss of response. By February 2014, he had clinically deteriorated to WHO FC IV and had evidence of peripheral oedema. Cardiac magnetic resonance (CMR) imaging was consistent with his WHO FC IV, demonstrating severe right ventricular (RV) dysfunction with an ejection fraction of 23%. There was no evidence of pleural effusion while he had a preserved left ventricular ejection fraction of 63%. Ambrisentan was switched to nebulised iloprost (5 µg; seven times per day), diuretics were increased but bosutinib was continued. Because of lack of clinical improvement, he was transitioned to domiciliary intravenous iloprost in March 2014. In June 2014, he was admitted to acute care in decompensated right heart failure with peripheral oedema, a new right-sided effusion and severe dilatation of the right-sided cardiac chambers with no left atrial enlargement on imaging. He was given further diuretics and required a chest drain. Bosutinib was discontinued. His PAH therapy was unchanged.

3 months following cessation of bosutinib, he had improved markedly being in WHO FC II and by 6 months his ISWD had increased to 600 m; *i.v.* iloprost was therefore discontinued and he was restarted on a combination of tadalafil and ambrisentan. CMR in December 2015 reflected his WHO FC II, demonstrating only mild RV impairment with a right ventricular ejection fraction (RVEF) of 48%.

In March 2016, he was commenced on ponatinib. He was reviewed after 6 weeks of treatment because he complained of worsening breathlessness. His PAH therapy was unchanged. His ISWD was unchanged at 460 m; however, symptomatically he was in WHO FC III. CMR was consistent with the worsening of his WHO FC, demonstrating significant deterioration compared with December 2015, with RV end-diastolic volume increasing from 157 to 220 mL, RVEF falling to 22% and the development of more pronounced paradoxical septal motion. There was no evidence of pleural effusions. Ponatinib was stopped and he awaits further review.

Although phase 1–3 studies identified possible PH as an adverse reaction in four out of 870 patients treated with bosutinib [3], to our knowledge this is the first published case report linking bosutinib with PAH. Different effects of TKIs on the pulmonary vasculature *in vitro*, animal models and humans have been described. Imatinib was shown to have possible beneficial effects in PAH in humans although,

because of a high rate of side-effects, most notably subdural haematomas, it has not been licensed. Although nilotinib-associated PAH has not been described, a randomised controlled trial of nilotinib in PAH was halted because of an increased risk of severe effects [4]. Dasatinib has been shown to reverse PAH in animal models; however, paradoxically dasatinib-associated PAH has been reported in the literature in at least 41 patients [5, 6]. The majority of described cases of dasatinib-associated PAH have resolved or significantly regressed on cessation suggesting a vasoconstrictive pathophysiology resulting in PAH; however, the patient in the current study had severe PAH at diagnosis despite previous cessation of dasatinib. A degree of clinical worsening was also observed while receiving nilotinib, although he responded well to the addition of a second PAH therapy despite nilotinib continuation. This worsening may have been related to persistence of dasatinib-induced vasculopathy, although an adverse effect of nilotinib cannot be discounted. Certainly, the severe deterioration we observed following commencement of bosutinib, and marked improvement on its cessation was much more clinically striking.

The kinase inhibition profile of each TKI is likely to play a key role in determining the net pulmonary vascular response. Nagaraj *et al.* [7] hypothesised that Src inhibition mediates the development of PAH after treatment with dasatinib or ponatinib and it is interesting to note that bosutinib, unlike imatinib and nilotinib, is also an inhibitor of Src. While Src has been implicated in the control of pulmonary vascular tone [7], *in vitro* data show that Src inhibition attenuates pulmonary artery smooth muscle cell proliferation and migration and reverses pulmonary arterial remodelling in both monocrotaline rat and hypoxic mouse models [8], while constitutive Src activation plays a role in endothelial dysfunction in the context of heritable PAH [9]. The paradoxical effects of TKIs observed in animal models and humans suggest that animal models are unreliable predictors of the consequence of therapeutic TKI use in patients with PAH. Further work exploring these factors and clarifying the mechanisms by which specific kinases alter pulmonary vascular cell phenotype is therefore warranted. Nevertheless, we strongly echo the recommendations by Quilot *et al.* [1] that clinicians monitoring patients on TKI therapies should have a low threshold for investigating for PAH in patients who develop progressive breathlessness.

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A patient with severe worsening of pre-existing PAH following treatment with bosutinib improved on cessation http://ow.ly/gJy7302uXL7

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