Pulmonary arterial hypertension exacerbated by ruxolitinib

The JAK 1 and 2 inhibitor ruxolitinib is the first drug licensed for the treatment of myelofibrosis and has transformed the management of this condition.[1,2] Pulmonary hypertension is a known complication of myelofibrosis,[3] but no link with ruxolitinib has previously been described. Here we report for the first time an association between worsening pulmonary arterial hypertension (PAH) and ruxolitinib, with improvement on withdrawal of the drug on two separate occasions. An association between PAH and a number of drugs is recognized[4] and its development results in considerable morbidity primarily due to breathlessness and reduced exercise tolerance. Symptoms may improve on withdrawal of the offending drug, but some patients will have persistent symptoms that require specific PAH drug treatment. Tyrosine kinase inhibitors (TKIs) are a diverse group of drugs, some of which are known to affect the pulmonary vasculature, and while some can induce PAH, others can improve pulmonary hemodynamics.[4,5] The JAK proteins are tyrosine kinase proteins whose role in PAH is unclear.

A 57-year old woman with a background of Budd-Chiari and portacaval shunt in the 1980s, testing positive for the *JAK2V617F* mutation, was entered into a treatment trial for progressive myelofibrosis (*clinicaltrials.gov identifier:* 01433445 phase Ib: panobinostat 10 mg 3 times a week on alternate weeks and ruxolitinib 10 mg twice daily). Pulmonary arterial pressures were mildly elevated on pre-treatment echocardiogram and right ventricle (RV) size and function were normal (Table 1). Her itching and splenomegaly improved, but after two weeks treatment she developed breathlessness not caused by anemia. This continued to progress and by six weeks she was also hypoxemic. An echocardiogram showed severe elevation of her PAP with severe RV dilatation and moderate dysfunction (Table 1). A subsequent right heart catheter demonstrated severe pre-capillary pulmonary hypertension (PH) (Table 1). Lung function tests showed mildly reduced gas transfer, while CT pulmonary angiogram and ventilation-perfusion scans were negative for pulmonary embolism. The panobinostat and ruxolitinib were stopped.

Three months later she was WHO functional class III with a 6-minute walk distance (6MWD) of 420 m. Her echocardiogram had improved with reduced pulmonary arterial pressures, reduced RV dilatation and RV function was now normal (Table 1). Her breathlessness was also improving and so PAH-specific therapy was not prescribed. By eight months her symptoms had returned to pre-treatment levels and she was WHO functional class II with a 6MWD of 480 m. She was also able to play badminton again. A repeat RHC demonstrated improved pulmonary vascular resistance and improved cardiac output nine months after stopping the panobinostat and ruxolitinib. However, she requested further therapy for worsening itching and splenomegaly. It was not clear which drug had been responsible, but her pharmacokinetic studies showed serum panobinostat levels significantly above those of the rest of the dosing cohort, possibly due to her portacaval shunt, while ruxolitinib levels were normal. Half-dose ruxolitinib was thus re-started under close observation and the

Table 1. Echocardiogram, right heart catheter and cardiopulmonary exercise test data obtained in relation to treatment received for myelofibrosis.

	First treatment regimen				Second treatment regimen			
Time	Oct 2012 2 weeks before treatment	Dec 2012 After 6 weeks treatment	Feb 2013 2 months after stopping treatment	Mar 2013 3 months after stopping treatment	Oct 2013 4 weeks before treatment	Dec 2013 After 6 weeks treatment	Mar 2014 After 6 weeks increased dose	Jul 2014 4 months after stopping treatment
Ruxolitinib (mg BD)	–	10	–	–	–	5	10	–
Panobinostat (mg[a])	–	10	–	–	–	–	–	–
Echocardiogram								
TR max velocity (m/s)	3.2	4.5	…	3.8	…	4.0	…	3.4
Peak PAP (mmHg)	43	89	…	65	…	68	…	51
TAPSE (mm)	27	27	…	28	…	26	…	24
RV size	Normal	Severe dilatation		Mod dilatation		Mild dilatation		Mild dilatation
RV function	Normal	Mod impaired		Normal		Mild impaired		Normal
Right heart catheter								
RAP (mmHg)	…	…	6	…	5	6	…	…
mPAP (mmHg)	…	…	42	…	46	43	…	…
PVR (WU)	…	…	8.2	…	6.3	6.0	…	…
PCWP (mmHg)	…	…	12	…	10	9	…	…
CI (L/min/m^2)	…	…	2.3	…	3.3	3.4	…	…
CPET								
VO_2 peak (ml/min/kg) (% predicted)		…	…	…	20.4 (85%)	15.8 (66%)	12.9 (56%)	19.6 (85%)
V_E/VCO_2	…	…	…	…	36.1	38.6	45.8	38.1
AT (ml/min/kg)	…	…	…	…	14.5	12.1	10.0	14.3
Oxygen saturation (%)	…	…	…	…	95 to 89	98 to 89	98 to 90	96 to 90

[a]*Panobinostat dosage – 10 mg 3 times a week on alternate weeks; AT: anaerobic threshold; BD: twice daily; CI: cardiac index; mPAP: mean pulmonary arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; VE/VCO2: minute ventilation to carbon dioxide production ratio; VO2: oxygen consumption; WU: Wood Units.*

patient was provided with a clear warning that she may develop worsening PAH again.

After one month her itching and splenomegaly had improved without increasing breathlessness. Though her exercise capacity on cardio-pulmonary exercise testing (CPET) had reduced, her right heart catheter findings were acceptable (Table 1), so the dose was increased. After six weeks she was markedly breathless on exertion again. Repeat CPET was consistent with worsening PAH and the ruxolitinib was stopped.

Four months later her breathlessness, echocardiogram and CPET had returned to baseline (Table 1). Unfortunately, her myelofibrosis symptoms have deteriorated and other therapies are being considered.

Until recently, myelofibrosis treatment was limited to allogeneic stem cell transplant or palliation. Aberrant JAK/STAT signaling plays a key role in its pathogenesis,[6] particularly JAK1 and 2 dysregulation.[7] The novel drug ruxolitinib inhibits JAK1 and 2, improving splenomegaly, disease-related symptoms, quality-of-life and survival.[1,2]

JAK/STAT signaling may be important in PAH as STAT3 activation causes upregulation of mediators that lead to proliferation and anti-apoptosis of pulmonary arterial smooth muscle cells (PASMC).[8] JAK proteins cause STAT activation, but the role of JAK activation in PAH is undetermined. Though in idiopathic PAH (IPAH), JAK2 inhibition reduces proliferation of pulmonary arterial endothelial cells,[9] JAK2 upregulation in PASMC has not been demonstrated.[10] Also, JAK2 gene expression is increased in PAH in limited cutaneous sclerosis, but not in IPAH.[11] JAK inhibition can also initiate compensatory pathways such as Src in other diseases such as non-small cell lung cancer,[8] so a paradoxical increase in STAT3 activity could occur. In addition, JAK1 and 2 are tyrosine kinase proteins,[12] and TKIs can have contrasting effects in PAH, with dasatinib potentially causing PAH,[4] while imatinib improves pulmonary hemodynamics and exercise capacity in IPAH.[5] The potential effect of JAK inhibition *in vivo* is thus unclear in PAH.

PH occurs in one-third of myelofibrosis patients[3] and in 2%-6% of portal hypertension patients.[4] While either could explain the mild elevation of pulmonary arterial pressures pre-treatment and the possibility of some residual PH after withdrawal, the temporal relationship with the trial drugs makes progression of pre-existing disease unlikely. The patient was not re-challenged with panobinostat on the second occasion and other histone deacetylase inhibitors reduce PAH in animal models[13] implicating ruxolitinib as the cause. Ruxolitinib may improve PH in myelofibrosis based on echocardiogram findings and serum BNP levels[14] but this has not been confirmed by right heart catheter, CPET or formal assessment of effects upon breathlessness. The lack of invasive hemodynamic data prior to initiation of ruxolitinib is a limitation of this case, but a right heart catheter was not performed as the patient was asymptomatic and no prior link between ruxolitinib and PAH had been described. However, PAH was confirmed on subsequent invasive testing, and pulmonary vascular resistance improved after ruxolitinib was stopped. This correlated with both improvements on echocardiogram and the patient's symptoms. The patient then became symptomatic on a second occasion when ruxolitinib was used at full dose with CPET evidence of worsening PAH suggesting this drug was the cause.

The etiology of PH in myelofibrosis is complex,[15] but includes mechanisms that augment venous thrombosis and mechanisms resulting in PAH-like disease, such as extramedullary hemopoiesis. While these may respond differently to ruxolitinib, our patient had no evidence of pulmonary embolism, and ruxolitinib reduces extramedullary hematopoesis. How ruxolitinib may exacerbate PAH is thus unclear. We recommend comprehensive and cautious monitoring of patients with known PAH who are to be treated with ruxolitinib.

To our knowledge this is the first case of PAH due to a drug affecting JAK/STAT signaling, specifically a JAK1 and 2 inhibitor. The mechanism is unclear; however, resolution was achieved by withdrawing the offending drug and PAH-specific therapy was not required.

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