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Case Report

Combination Therapy With Pulmonary Vasodilatation and JAK2 Inhibition for Pulmonary Hypertension With Polycythemia Vera

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Pulmonary hypertension (PH) associated with polycythemia vera (PV) can result from various conditions. Few case reports of patients with PV and PH have described drug treatment with PH-targeted drugs, and its effect remains unknown. Ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, has been reported to improve PH associated with increased nitric oxide levels. We present a case of a 70-year-old woman with PV and PH, which had multiple etiologies, including cardiopulmonary comorbidities, treated with combination therapy of riociguat and macitentan and a JAK1/2 inhibitor, leading to improvement of both her pulmonary hemodynamics and her REVEAL 2.0 risk score.

Case

A 70-year-old woman with well-controlled PV who was receiving hydroxyurea treatment (hemoglobin level:12.5 g/dL; white blood cell count: 3500 /mcL; platelet count: 295,000/mcL) presented with worsening dyspnea (World Health Organization functional class IV). The patient had had comorbidities, such as permanent atrial fibrillation and chronic obstructive pulmonary disease, and had received an inhaled long-acting muscarinic antagonist and a beta 2 agonist and long-term oxygen therapy for the preceding 6 months because of hypoxemia (air blood gas test; pO2: 50.7 mm Hg; pCO2: 30.5 mm Hg). The patient was admitted due to worsening dyspnea and was diagnosed with congestive heart failure (HF) and atrial fibrillation without rapid ventricular response, by clinical manifestations and imaging modalities, including computed tomography, which showed pulmonary edema (ie, ground-glass opacities) due to left HF. Iron deficiency was not observed. Transthoracic echocardiography revealed preserved left ventricular ejection fraction (63%), severe tricuspid regurgitation, and dilatation of the left atrium (left atrial volume index: 63.7 mL/m^2). Right heart catheterization revealed the following: combined pre- and post-capillary pulmonary hypertension (PH; mean right atrial pressure, 19 mm Hg; mean pulmonary arterial pressure [mPAP], 36 mm Hg; pulmonary arterial wedge pressure [PAWP], 16 mm Hg; pulmonary vascular resistance [PVR], 7.9 Wood units; and diastolic pressure gradient, 8 mm Hg; Fig. 1). Follow-up right heart catheterization, after achieving euvolemia by using diuretics, on the 25th day showed a sustained increase in the mPAP (35 mm Hg) and PVR (14.7 Wood units), despite a decrease in the PAWP (6 mm Hg), revealing a shift from combined pre- and post-capillary PH to pre-capillary PH (Table 1; Fig. 1; Supplemental Table S1). The severity of chronic obstructive pulmonary disease was not proportional to that of PH (computed tomography showed centrilobular emphysema with predominantly upper lobe involvement). No severe bullae or fibrosis was found; forced expiratory volume in 1 second as a percentage of forced vital capacity was 66.8%; forced vital capacity was 104.1%; total lung capacity was 128.6%; diffusing capacity of lung for carbon monoxide was 30.1%; diffusing capacity of lung for carbon monoxide, corrected alveolar volume was 26.0%). Bone marrow examination revealed marked hypercellular marrow and mild fibrosis, which indicated progression to post-polycythemic myelofibrosis. Genetic analysis revealed a mutation in the Janus kinase 2 (JAK2) gene (*JAK2*V617F), a common abnormality in

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Ethics Statement: The patient provided informed consent for the preparation of this report.

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Novel Teaching Point

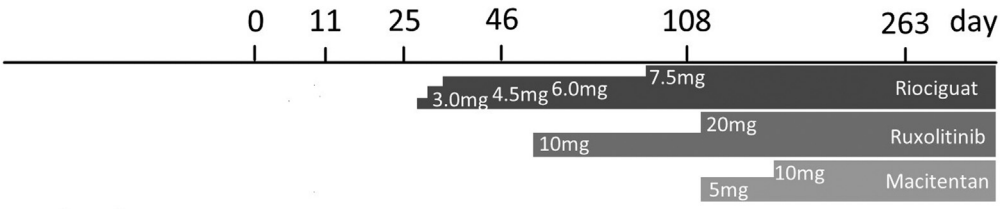
- Clinical findings of pulmonary arterial hypertension, which may improve by PH-targeted drugs, could be overlooked in patients with well-controlled PV, because of noticeable clinical manifestations and findings of left heart failure.

PV; most cases are positive for this mutation.[1] After ruling out connective tissue diseases, chronic thromboembolic pulmonary diseases by pulmonary ventilation-perfusion scan, and other systemic diseases, the patient was diagnosed with combined pre- and post- capillary PH, most likely a consequence of PV, based on studies showing that both types are linked to PV.[2] Given that the clinical characteristics were compatible with pulmonary arterial hypertension, monotherapy with riociguat, off-label for PV, was initiated on the 26th day. Furthermore, ruxolitinib, a JAK1/2 inhibitor, was added as a sequential combination therapy on the 53rd day because riociguat improved hemodynamic parameters, such as PVR and cardiac index, but did not affect the risk score, which remained high (World Health Organization functional class IV to III; mPAP, 34 to 35 mm Hg; PVR, 14.7 to 6.7 Wood units; **R**egistry to **Ev**aluate **E**arly **a**nd **L**ong-term Pulmonary Arterial Hypertension Disease Management [REVEAL] 2.0 score, 15 to 13 points). Given that the patient remained at high risk (13 points), macitentan, off-label for PV, was further added, and the dosage of ruxolitinib was increased from 10 mg to 20 mg daily on the 109th day. Combination therapy with PH-targeted drugs and ruxolitinib finally improved the REVEAL 2.0 score (6 points) without worsening left-sided HF on the 263rd day (Fig. 1). Oxygen requirements did not increase after the initiation of these drugs. The arterial oxygen partial pressure levels on the 11th and 263rd day were 51.4 (oxygen flow rate: 4 L/min) and 79.2 (oxygen flow rate: 2 L/min) torr, respectively. During the 19-month follow-up after hospital discharge, no HF deterioration was observed.

Discussion

Observational studies have shown that myeloproliferative neoplasms (MPNs), including PV, are associated with PH. A recent evaluation of hemodynamic parameters among patients with PV and suspected PH revealed PH in approximately 80% of patients, pre-capillary PH in 30% of patients, and post-capillary PH in 50% of patients.[2] Due to various mechanisms of PH development in PV, such as chronic thromboembolic PH, pulmonary arteriopathy, and left HF diseases,[1] the ideal therapeutic approach among patients with PH and PV has not been established.

In a case report of a PV patient with pulmonary veno-occlusive disease (PVOD), PH-targeted drugs caused pulmonary edema.[3] In our case, oral dual therapy with riociguat and macitentan was cautiously initiated after confirming the



mPAP (mmHg)	36	35	35	31	27
sPAP (mmHg)	56	68	54	46	46
dPAP (mmHg)	24	23	21	22	15
PVR(Wood units)	7.9	14.7	6.7	7.7	3.8
PAWP (mmHg)	16	6	12	11	13
RAP (mmHg)	19	5	7	12	7
DPG (mmHg)	8	17	9	11	2
CI (L/min/m²)	1.8	1.6	2.7	2.0	2.8
RVSWI (g/m/beat/m²)	4.5	9.1	13.0	6.7	12.7
PAPi	1.7	9.0	4.7	2.0	4.4
6MWD (m)			234	300	340
BNP (pg/mL)	234.9	158.4	111.0	63.3	47.8
WHO-FC	IV	III	III	III	II
Systolic BP; HR	92; 89	96; 71	92; 78	93; 76	112; 61
Pericardial effusion	+	+	-	-	-
REVEAL 2.0 score	17	15	13	13	6

Figure 1. Clinical time-course changes in the present case. Cardiac output was measured by using the indirect Fick method. 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; BP, blood pressure; CI, cardiac index; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; HR, heart rate; mPAP, mean pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, **R**egistry to **Ev**aluate **E**arly **a**nd **L**ong-term Pulmonary Arterial Hypertension Disease Management; RVSWi, right ventricular stroke work index; sPAP, systolic pulmonary artery pressure; WHO-FC, World Health Organization functional class.

Table 1. Left heart disease risk factors and clinical time-course changes in cardiac medications, except pulmonary hypertension (PH)-targeted medications

Left heart disease risk factors	
Atrial fibrillation	(+)
Body mass index	16.9 (the 25th day)
Hypertension	(−)
Diabetes mellitus	(−)
Coronary artery disease	(−)

Clinical time-course changes in cardiac medications except PH-targeted medications

		Day				
	Before admission	**11**	**25**	**46**	**108**	**263**
Furosemide, mg	40	60	20	20	20	20
Spironolactone, mg	50	50	0	0	0	0
Tolvaptan, mg	0	0	3.75	3.75	7.5	7.5
Bisoprolol, mg	5	5	2.5	1.25	1.25	0
Digoxin, mg	0	0	0	0	0	0.125
Dobutamine, mcg/kg/min	0	3	0	0	0	0

Administration of furosemide was switched from oral to intravenous on admission. Furosemide infusion was started at 40 mg daily and increased to a maximum of 60 mg. Furosemide was switched from intravenous to oral 20 mg daily on the 17th day. Spironolactone was discontinued due to hyperkalemia on the 21st day. Tolvaptan was started at 3.75 mg daily on the 12th day and increased to 7.5 mg daily on the 109th day. Bisoprolol had switched to digoxin 0.125 mg daily on the 109th day.

absence of PVOD-specific computed tomography imaging, such as centrilobular ground-glass opacities or intralobular septum thickening. The partial improvement of PH by pulmonary arterial hypertension-specific pharmacotherapy suggests that nitric oxide (NO) deficiency and increased endothelin activation within pulmonary vessels could partly cause PH in PV and could be a therapeutic target for these patients.

JAK1/2 inhibition could be a novel target for managing PH-associated PV. In a case series of 15 patients with MPNs and PH, ruxolitinib, a JAK1/2 inhibitor (median 10 mg [minimum, 5 mg; maximum, 20 mg]), improved PH and was associated with an increase in NO levels.[4] In a case report of an active hematopoietic state PV patient with PVOD, ruxolitinib improved hemodynamics and hematopoiesis.[3] We firstly aimed for optimal activation of the NO—soluble guanylate cyclase—cyclic guanosine monophosphate pathway to reduce right ventricular afterload and increase cardiac output because of severely impaired pulmonary hemodynamics. Riociguat reduced PVR by half of the baseline, but the risk category remained high, and we expected that adding ruxolitinib would enhance cyclic guanosine monophosphate stimulation by activating NO levels. In our case, PH did not improve with 10 mg/d of ruxolitinib, but it improved after a 20 mg/d dose, with the addition of macitentan. Differentiating the effect of ruxolitinib escalation from that of macitentan initiation is difficult, because both are performed at nearly the same time. To our knowledge, no previous case reports have used these treatments in patients with PH and PV. Although the precise mechanism of the limited effect of a JAK1/2 inhibitor on pulmonary circulation in our case remains unknown, several are possibilities. First, our case was not hematopoietic in nature. Second, pretreatment with riociguat, which activates the downstream target of NO, might attenuate the NO-dependent effect of JAK inhibition. Because the question of whether ruxolitinib had an effect, vs the PH-targeted drugs, remains unanswered, we would suggest repeating the right heart catheterization before adding more therapy.

Due to the increased PAWP in this case, we carefully chose a therapeutic strategy considering the involvement of left ventricular diastolic dysfunction, which was common in patients with MPNs.[5] As PH-targeted drugs could worsen pulmonary hemodynamics in patients with left ventricular diastolic dysfunction, we initiated sequential therapy with 2 PH-targeted drugs under euvolemic status, improving PH. As increased PAWP could be caused partly by the interaction between the right and left ventricle due to PH, we need to consider the balance between the benefits and risks expected from using PH-targeted drugs among patients with multifactorial PH.

In conclusion, this is the first report of sequential combination therapy with multiple PH-targeted drugs and a JAK2 inhibitor, leading to adequate improvement of pulmonary hemodynamics and risk category in patients with PV and PH.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2022.11.007.