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► To cite this version:

Carmel Bergbaum, Chinthaka Samaranayake, Alex Pitcher, Emma Weingart, Thomas Semple, et al.. A case series on the use of steroids and mycophenolate mofetil in idiopathic and heritable pulmonary veno-occlusive disease: is there a role for immunosuppression?. *European Respiratory Journal*, 2021, 57 (6), pp.2004354. 10.1183/13993003.04354-2020 . hal-04532503

HAL Id: hal-04532503

<https://hal.science/hal-04532503v1>

Submitted on 30 Oct 2024

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Early View

Research letter

The use of steroids and mycophenolate mofetil in idiopathic and heritable pulmonary veno-occlusive disease: A case series: Is there a role for immunosuppression?

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Please cite this article as: Bergbaum C, Samaranayake CB, Pitcher A, *et al.* The use of steroids and mycophenolate mofetil in idiopathic and heritable pulmonary veno-occlusive disease: A case series: Is there a role for immunosuppression?. *Eur Respir J* 2021; in press (<https://doi.org/10.1183/13993003.04354-2020>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

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The use of steroids and mycophenolate mofetil in idiopathic and heritable pulmonary veno-occlusive disease: A case series: Is there a role for immunosuppression?

Short title/running head: Immunosuppression improved idiopathic and heritable PVOD

In draft for ERJ, Research Letter

Word limit 1996/1200 words

Author list

Carmel Bergbaum^{1*}, Chinthaka B Samaranayake^{1*}, Alex Pitcher², Emma Weingart², Thomas Semple³, Maria Kokosi^{4,5}, Athol U Wells^{4,5}, David Montani⁶, Konstantinos Dimopoulos^{1,5}, Colm McCabe^{1,5}, Aleksander Kempny^{1,5}, Carl Harries¹, Elizabeth Orchard², S John Wort^{1,5}, Laura C Price^{1,5}

* Contributed equally

Affiliations

1. National Pulmonary Hypertension Service, Royal Brompton Hospital
2. Pulmonary Hypertension Unit, John Radcliffe Hospital, Oxford
3. Department of Radiology, Royal Brompton Hospital
4. Interstitial Lung Disease Unit, Royal Brompton Hospital
5. National Lung and Heart Institute, Imperial College London, London
6. Université Paris–Saclay, AP-HP, INSERM UMR_S 999, Department of Respiratory and Intensive Care Medicine, Hôpital de Bicêtre, Le Kremlin Bicêtre, France.

Corresponding Author

Laura C Price PhD FRCP

Consultant Respiratory Physician

National Pulmonary Hypertension Service, Royal Brompton Hospital

Royal Brompton Hospital

Sydney Street

London SW3 6NP, UK

Email: laura.price@rbht.nhs.uk

Conflicts of interest: Nil

Abbreviation list

6MWT	Six minute walk test
BNP	Brain natriuretic peptide
CO	Cardiac output
CTD	Connective tissue disease
FEV ₁	Forced expiratory volume in one second
FVC	Forced vital capacity
KCO _c	Carbon monoxide coefficient
mPAP	Mean pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure

Peak $\dot{V}O_2$	Peak oxygen uptake
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
RHC	Right heart catheter
$\dot{V}E/\dot{V}CO_2$	Ventilation/carbon dioxide production slope
TLCO _c	Transfer factor for carbon monoxide
WU	Wood units
VQ scan	Ventilation perfusion scan

Pulmonary veno-occlusive disease (PVOD) is classified into idiopathic, heritable and associated with other conditions, most often connective tissue disease (CTD) and sarcoidosis. In patients with PVOD with a CTD, immunosuppressive therapies can improve symptoms, gas transfer, imaging and haemodynamics.^{1,2} Despite evidence for inflammation in PVOD pathophysiology,^{3,4} including capillary immune complex and complement deposition,⁵ the role for immunosuppression in idiopathic or heritable forms of PVOD is uncertain. We present three patients with heritable and idiopathic PVOD who received immunosuppression for suspected immune dysregulation.

Case 1:

A 33-year-old lady presented with an 8-year history of progressive breathlessness. She had no past medical or drug history and had never smoked. Her maternal grandmother died from 'heart failure' in her thirties. She had no CTD. At baseline, she was in World Health Organisation (WHO) functional class III, with a six-minute walk test (6MWT) distance of 75m, desaturating to 81% on air by the end of the test. Echocardiography demonstrated right ventricular dilation, hypertrophy and moderately impaired function (tricuspid annular plane systolic excursion 1.8

cm, fractional area change 27%). Brain natriuretic peptide (BNP) was mildly raised at 25ng/L. Baseline lung function tests showed normal spirometry (forced expiratory volume in 1 second (FEV₁) 94% predicted, forced vital capacity (FVC) 94% predicted) with very low gas transfer (transfer factor for carbon monoxide (TLCO_c) 24% predicted, carbon monoxide coefficient (KCO_c) 22% predicted). Right heart catheterisation (RHC) at presentation demonstrated a mean pulmonary artery pressure (mPAP) 41mmHg, pulmonary artery wedge pressure (PAWP) 6mmHg, cardiac output (CO) 4.2L/min and pulmonary vascular resistance (PVR) 8.3 Wood units (WU), without vasoreactivity to inhaled nitric oxide. She was initially diagnosed with idiopathic pulmonary arterial hypertension (PAH) and commenced on sildenafil, then the endothelin receptor antagonist ambrisentan. Despite an initial brief improvement in breathlessness and 6MWT distance, she had progressive marked fatigue and exercise intolerance over the next three years. Repeat RHC showed persistent PAH (Table 1), and cardiopulmonary exercise (CPET) testing revealed a very low peak oxygen uptake ($\dot{V}O_2$, 34% of predicted) with poor ventilatory efficiency: ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) slope 56. High-resolution computed tomography (HRCT) of the chest showed more widespread thickening of interlobular septa compared to the previous scans typical of PVOD, and repeat lung function showed persistently low gas transfer (Table 1). The diagnosis of PVOD was further supported by a homozygous *EIF2AK4* mutation, and she was referred for lung transplantation. Due to progressive worsening of her respiratory status and profound fatigue, often associated with immune dysregulation, a trial of immunosuppressive therapy with pulsed intravenous methylprednisolone then oral prednisolone was initiated. Breathlessness symptoms and oxygen saturations improved. With reduction in oral steroid dose, symptoms worsened. Immunomodulation was therefore continued, with addition of mycophenolate mofetil (titrated to 1g twice a day) to low-dose oral prednisolone. Twelve-months after initiating immunosuppression, 6MWT distance increased to 440m, TLCO_c and CPET indices improved, invasive haemodynamics near-normalised (Table 1), and HRCT showed improvements in

interlobular septal thickening. Therefore, the patient stepped down to the 'watch and wait' transplant list and remains stable six years after the initial diagnosis of PAH.

Case 2:

A 57-year old lady presented with progressive breathlessness over a two-year period. Lung function testing showed normal spirometry (FEV_1 103% and FVC 113% predicted), however gas diffusion was very low ($TlCO_c$ 28% and KCO_c 28.2% predicted). Initial 6MWT distance was 465m, with marked oxygen desaturation (pre-test 92% and post-test 79%). Contrast echocardiogram was consistent with intra-pulmonary shunting, likely due to intussusceptive neoangiogenesis of pulmonary capillaries.⁶ Chest CT showed ground glass changes, centrilobular nodules and mild mediastinal lymphadenopathy. A complete CTD screen was negative. Genetic testing was not performed in this patient. Right heart catheterisation study demonstrated PAH (mPAP 32mmHg, PAWP 9mmHg, CO 3.0 L/min and PVR 7.7 WU) without vasoreactivity to inhaled nitric oxide. A multidisciplinary consensus diagnosis of PVOD was made, and she was started on sildenafil and then bosentan. Due to ongoing deterioration in symptoms and declining gas-diffusion, immunosuppression with pulsed intravenous methyl prednisone followed by mycophenolate mofetil (titrated to 1g twice a day) was introduced. Clinical parameters improved (Table 1), and the ground glass changes and centrilobular nodules resolved on a follow-up CT scan. She remains stable three years after initiation of immunosuppression.

Case 3:

A 39-year old previously fit-and-well man with a family history of PAH was investigated for mild breathlessness on exertion. Lung function testing showed normal spirometry (FEV_1 115% and FVC 119% predicted), however gas-diffusion was low ($TlCO_c$ 44.5% and KCO_c 39.6% predicted). His 6MWT distance was normal at 700m, however there was oxygen desaturation

(pre-test 99% and post-test 85%) on exertion. Echocardiography showed normal RV size and function, and with positive delayed bubble study. Cardiac magnetic resonance imaging excluded intracardiac shunts. There were no significant mismatched defects on a VQ scan. High-resolution CT scan of the chest was unremarkable with no features of interstitial lung disease. Complete CTD screen was negative. Resting pulmonary haemodynamics were within normal limits (Table 1). On invasive CPET testing, there was evidence of PAH (peak exercise mPAP 47mmHg, PCWP 13, CO 14.8 L/min, total pulmonary resistance 3.2 WU) and exercise ventilatory inefficiency ($\dot{V}E/\dot{V}CO_2$ 42). A surgical lung biopsy showed occlusive microvasculopathy affecting both small arterioles and venules. There was preservation of alveolar architecture, with patchy capillary congestion, mild cellular and sclerotic fibrointimal thickening in places, associated with a mild lymphocytic infiltrate. Genetic screening for mutations associated with PAH, including *EIF2AK4*, was negative. A multidisciplinary consensus diagnosis of early PVOD was made, and due to progressive exertional symptoms, he was commenced on treatment with mycophenolate mofetil and low-dose prednisolone. At 24 months follow-up, he remains stable.

Discussion

We present three cases of heritable and idiopathic PVOD where immunosuppression using mycophenolate and prednisolone stabilised symptoms, oxygenation, gas transfer and haemodynamic parameters. To our knowledge, this is the first such case series reported. Clinical and haemodynamic improvement with glucocorticoids and antimetabolites has been described in *CTD-associated* PVOD,^{1,2} and transiently with steroids in mitomycin-induced PVOD.⁷ Whether the treatment effect observed in our patients and in those previously described is due to the same process is unclear. However, it is possible that immunosuppression leads to downregulation of inflammatory processes implicated in PVOD.³ In a mitomycin-induced PVOD model of chemotherapy-induced PVOD, severe intimal lesions of small pulmonary veins were

associated with extensive adventitial accumulation of eosinophils,⁸ although this is not seen in PVOD autopsy specimens. This supports the hypothesis that inflammation may be more relevant early in PVOD pathophysiology, akin to the response to immunosuppression seen in patients with systemic lupus erythematosus and mixed CTD-associated PAH in early disease.⁹ Additionally, the *EIF2AK4* mutation, the major cause of heritable PVOD,¹⁰ may be pro-inflammatory, leading to loss of the general control nonderepressible 2 (GCN2) protein,^{4,11} a serine/threonine kinase whose absence increases oxidative stress.^{4,12} In this report, the patient with the *EIF2AK4* mutation benefited most from immunosuppression.

No established medical therapy exists for PVOD. Pulmonary vasodilators can stabilise haemodynamics, at least until lung transplantation, but may induce pulmonary oedema.^{4,13,14} There is early clinical evidence of imatinib, a tyrosine kinase inhibitor, having beneficial effects as a bridge to transplantation.¹⁵ Lung transplantation remains the only curative treatment for PVOD,¹⁶ and prompt referral remains essential.

Prognosis for patients with PVOD is poor.¹⁷ Given the clinical improvement and/or stability in these cases, and evidence of immune dysregulation driving pathophysiology, further understanding of the role of immunosuppression in PVOD is key.

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Variable	Case 1		Case 2		Case 3	
	Pre pred./MMF	Post pred./MMF	Pre pred./MMF	Post pred./MMF	Pre pred./MMF	Post pred./MMF
WHO FC	III	II	III	II	I	I
Medications	Sildenafil Ambrisentan	Sildenafil Ambrisentan	Tadalafil Bosantan	Tadalafil Bosantan	Nil	Nil
PAH Therapy						
Duration of PAH therapy	3 years	4 years	1 year	2 years	-	-
MMF Dose		750mg BD		1g BD		500mg BD
Other immunosuppression		Pred 7.5mg		Pred 7.5mg		Pred 7.5mg
6MWT						
Distance (m)	190	440	465	420	700	
O ₂ flow rate (L/min)	4	4	On air	On Air	On air	
O ₂ saturations (pre, %)	94	97	92	91	99	
O ₂ saturations (post, %)	90	97	79	77	85	
TTE						
LVEF (%)	66	Good	60%	70%	63%	65%
RV size	Normal	Upper normal	Normal	Normal	Normal	Normal
RV function	Impaired	Good	Normal	Normal	Normal	Normal
TDI S' (cm/s)	-	-	14	12.4	15	13.4
TAPSE (cm)	-	-	1.7	2.4	2.3	2.5
BNP (ng/L)	49	15	72	33	10	6
Right heart catheter						
RAP (mmHg)	3	-	6	5	4	4
mPAP (mmHg)	45	24	32	28	23	22
PAWP (mmHg)	11	12	9	6	9	6
CO (L/min)	4.7	4.0	2.97	2.75	6.5	7.13
PVR (WU)	7.7	2.1	7.7	8.0	3.0	2.3
CPET						
Peak VO ₂ (ml/kg/min)	11.3	14.0	-	-	28.6	32.1
VE/VCO ₂	56	45	-	-	46	34.1
Peak RER	0.95	1.1	-	-	1.4	1.2
PFTs						
FEV1 (%)	93	102.2	103	93.7	119	120
FVC (%)	100	111.9	113	105.3	123	121
FEV1:FVC (%)	82	82.3	76.1	74.8	80	79.7
DLCO (mmol/min/kPa %)	24	37.3	28	29.6	43	48.3
KCO (mmol/min/kPa/L [%])	30	40.0	28.2	29.7	40	44.1

Pred. prednisolone; MMF: mycophenolate mofetil; WHO FC: World Health Organisation Functional Class; Pred: Prednisone; 6MWT: Six minute walk test; TTE: transthoracic echocardiogram; LVEF: left ventricular ejection fraction; RV: right ventricle; BNP: brain natriuretic peptide; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; PVR: pulmonary vascular resistance; WU: Wood units; CPET: cardio-pulmonary exercise test; peak VO_2 : peak oxygen uptake; VE/VCO_2 : ventilation efficiency/carbon dioxide production; RER: respiratory exchange ratio; PFTs: pulmonary function tests; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; KCO: carbon monoxide transfer coefficient