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Use of pulmonary arterial hypertension therapies in patients with sarcoidosis-associated pulmonary hypertension

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To the Editor,

The development of pulmonary hypertension (PH) in patients with sarcoidosis (SAPH) is a feared complication, associated with exercise intolerance, increased oxygen requirement, impaired quality of life (1) and increased mortality (2), especially in patients with pre-capillary PH (3).

Patients with SAPH may present with several 'PH phenotypes' including sarcoid vasculopathy, lung fibrosis with parenchymal destruction, chronic thromboembolic disease, left sided heart disease and compressive vascular phenotypes (4), with rationale although little evidence supporting guidelines to use pulmonary arterial hypertension (PAH) therapies in patients with pre-capillary PH (5). Placebo-controlled trials of bosentan show improved hemodynamics but not 6-minute walk distance (6MWD) (6); and suggest that riociguat reduced clinical worsening (7). We investigated the real-world use of PAH therapies in patients with SAPH using registry data from UK and US centres.

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Methods

Patients with SAPH diagnosed between 1st January 2008 and 31st December 2021 treated with PAH therapies were studied from London (UK), Temple University Hospital, Philadelphia (USA) and Fairfax (Fall's Church, Virginia, USA). PH was diagnosed by criteria applicable to that period, with mean pulmonary artery pressure (mPAP) ≥25 mmHg, pulmonary capillary wedge pressure (PCWP) ≤15mmHg and pulmonary vascular resistance (PVR) >3 Wood units (WU)) (8). Prospective ethical approval was in place for data sharing (approval IRAS no 162717, REC number 15/NE/0044).

Baseline and follow up assessment

Patients were assessed at baseline prior to starting PH therapy until death/transplantation/end of the study. Follow up data were collected at baseline first assessment (prior to baseline right heart catheterisation (RHC), before initiation of PAH therapy) and 3-6 months after treatment initiation. Clinical assessment included WHO functional class, quality of life score (emphasis-10, E10), brain natriuretic peptide (BNP), pulmonary function testing, six-minute walk distance and RHC data.

Statistical methods

Data are mean ± standard deviation (SD) for normally distributed variables and median (range or interquartile range (IQR)) for non-parametric data. A p-value <0.05 was considered significant. Survival analysis was restricted to UK patients, from the date of entry into the registry (prior to baseline RHC) until December 31, 2021, death or lung transplantation. Patients lost to follow-up were censored at the last visit. Cox proportional hazards analysis examined the association between survival and baseline variables. Analyses used STATA (version 13.1).

Results

202 patients were identified; patients were excluded due to missing RHC data (n=39), group 2 PH (n=14), CTEPH (n=5), not on PAH therapies (n=18), or died before starting PAH treatment (n=2). A total of 124 patients with pre-capillary SAPH who received PAH therapies were eligible: London, UK (n=80), Fairfax, USA (n=34) and Cincinnati, USA (n=10). Compared to US, UK patients were more often white, males, with Scadding stage 4 disease, and with more severe gas transfer impairment (Table 1).

A total of 82 (66%) patients were treated with PH monotherapy at any time, 42 (34%) received sequential dual combination therapy, with addition of an additional treatment at median (range) 6.6 (2-26) months (dates available in n=37), and one (1%) received triple combination PH therapy. There were no significant differences in age, sex, WHO FC, lung function or haemodynamic parameters between patients receiving monotherapy vs. combination therapy, for example age (61±7.8 vs 58±11 years, p=0.18), %FVC (61.6±19 vs 64.5+-19 %, p=0.5), % DLCO (27.7±13.1 vs 26.6±12.7 %, p=0.7) RAP (7.8±5.8 vs 6.8±4.3mmHg, p=0.8), mPAP (40.1±10.5 vs 43.3±10.9mmHg, p=0.2) and PVR (8.8±4.5 vs 9.2±4.5 Wood units, p=0.6).

Of those receiving monotherapy, 62 (76%) had initial therapy with a PDE5i (91% sildenafil, 9% tadalafil; 19 (23%) patients were treated with an endothelin receptor antagonist: 75% bosentan, 16% macitentan, 9% ambrisentan. Two US patients received riociguat (one as monotherapy); 3 were on selexipag in combination with a PDE5i (n=2) or riociguat (n=1). Small numbers received prostanoid therapy: there were two patients on inhaled iloprost (UK n=1, US n=1), and three patients on IV epoprostenol (US only), either as dual with a PDE5i (2) or monotherapy (1).

Complications of treatment included dizziness (n=1), muscle cramps (1), reversible hearing loss (n=1), visual blurring which improved with dose reduction (n=1) with PDE5i, facial swelling (1), leg swelling (1) and increased dyspnoea (n=1) with ERA. No intolerance was reported with prostanoids. Serial oxygen saturations (n=54, paired) showed stability from median (IQR) 94 (92.8-97.3) to 95 (93-97) % (p=0.74) at first follow up.

Treatment responses

At first follow-up, following initiation of PAH therapies (3-6 months after therapy initiation), 6MWD was unchanged from 287 (180-371) to 277 (200-368) m (p=0.89, n=68). BNP declined from 73 (27-282) to 46 (21-167) ng/L (p=0.02, n=91). Hemodynamics (only available in n=32 (26%)) observed a decline in mPAP (39.1±9.2 to 36.1±11.6 mmHg, p=0.04) but no change in CO (4.6±1.7 to 4.6±1.2 l/min, p=0.4), RAP (6.7±4.8 to 5.2±4.1 mmHg, p=0.06) or PVR (7.42±4.3 to 6.8±4.0 Wood units, p=0.45). Emphasis10 quality of life, measured only in the UK cohort, worsened from 24.9 ± 2.23 to 33.5 ± 2.0 (p=0.02, n=57).

Survival

Due to differences in follow up periods, only UK patients were analyzed for survival. There were 22/80 UK deaths during the study period, and one patient was transplanted in 2012. Overall transplant-free survival at 1, 3 and 5 years was 92%, 76% and 54% respectively. Unadjusted and adjusted Cox analysis is shown in Table 2.

Discussion

In the UK cohort, patients were more often male, white, with more lung fibrosis, more severe PH and more functional impairment, highlighting differences in referral patterns and prescribing practices compared to the US (2). PAH therapies were generally well tolerated in both cohorts, without a significant change in oxygenation. Median survival rates in the UK PH treated patients were akin to a French sarcoid-PH registry (9) where mortality was

Table 1. Comparison of baseline demographic, pulmonary haemodynamic and treatment approach in patients with sarcoidosis-associated pulmonary hypertension, in US and UK centres.

	Total n=124	**UK n=80**	**US n=44**	**p value**
Age (years), mean ± S.D	58.8 ± 9.9	59.8 ± 9.3	57.1 ± 11.1	0.16
Sex (%male)	46 (37.1)	35 (44%)	11 (25%)	0.04
BMI (kg/m^2), mean (SD)	28.8 ± 7.4	26.4 (5.3)	33.1 (8.5)	<0.0001
Ethnic origin:				
White, n (%)	51 (41.1)	39 (48.8%)	12 (27%)	p<0.0001
Black, n (%)	55 (44.4)	23 (28.8%)	32 (72%)	
Asian/Indian/Other, n (%)	8 (6.5)	18 (10.0%)	0	
Missing, n (%)	10 (8.1)	10 (12.5)	0	
Scadding stage (n=119)				
0	4 (3.4)	0	4 (9.8)	p<0.0001
1	1 (1)	0	1 (2.4)	
2	5 (4.2)	2 (2.6)	3 (7.3)	
3	18 (15.1)	6 (7.7)	12 (28.3)	
4	91 (76.5)	70 (89.7)	21 (51.2)	
WHO I/II, n (%)	33 (26.6)	7 (8.7)	26 (59.1)	<0.001
WHO III/IV, n (%)	80 (64.5)	72 (90.0)	8 (18.2)	0.0007
WHO missing, n (%)	11 (8.9)	1 (1.3)	10 (22.7)	0.0002
6MW, m, mean ± SD	274±145m	210 (142-300)	350 (282-484)	
6MW missing, n (%)	31 (25.0)	23 (29)	3 (7)	
BNP, ng/l, median (IQR)	73 (27-282)	118 (44-374)	28 (12-70)	
BNP missing, n (%)	41 (33.1)	14 (18)	16 (36)	
Emphasis10, mean ± SD	24.5 ± 16.8	24.5 ± 16.8	(UK data only)	
RHC, mean ± SD				
RAP, mmHg	7.4 ± 5.0	7.4 ± 5.2	7.5 ± 4.8	0.94
mPAP, mmHg	39.1 ± 10.5	41.4 ± 10.7	34.9 ± 8.6	0.0007
PCWP, mmHg	10.4 ± 5.4	10.1 ± 5.5	11.1 ± 5.3	0.34
CO, l/min	4.6 ± 1.7	3.9 ± 1.1	5.7 ± 1.9	0.0001
Cardiac index, l/min/m^2	2.4 ± 0.7	2.2 ± 0.5	2.8 ± 0.7	0.0001
PVR, Wood units	7.4 ± 4.3	8.9 ± 4.5	5.1 ± 2.5	0.0001
Lung function, mean (SD)				
FEV1, litres (L)	1.4 ± 0.6	1.3 ± 0.6	1.5 ± 0.59	0.04
FEV1 % predicted (pred.)	52.6 ± 19.3	49.5 ± 15.5	57.0 ± 23.2	0.04
FVC, L	2.1 ± 0.85	2.1 ± 0.95	2.2 ± 0.71	0.36
FVC, % pred.	63.3 ± 19.7	62.8 ± 18.9	64.1 ± 21.0	0.76
FEV/FVC %,	0.76 ± 0.19	0.8 ± 0.2	0.7 ± 0.14	0.02
DLCO %pred.	33.0 ± 17.6	27.2 ± 12.8	43.5 ± 20.3	0.0001
KCO %pred.	48.7 ± 14.3	48.7 ± 14.3		
Lung function missing, n (%)	2	2	0	
PH therapy, n (%)				
Monotherapy only	82 (66)	48 (60)	34 (77)	0.04
Combination (dual/triple)	42 (34)	32 (40)	10 (23)	
Combination therapy, n (%)				
PDE first	37 (88)	29 (91)	8 (80)	0.0001
ERA first	5 (12)	3 (9)	2 (20)	
Immunosuppression, n (%)				
Oral steroids (N=118)	91 (77)	59 (76)	32 (80)	0.59
MMF (N=82)	27 (34)	25 (31)	2 (11)	0.03
Azathioprine (N=94)	25 (27)	14 (18)	11 (79)	0.0001
Methotrexate (N=109)	18 (17)	9 (11)	9 (31)	0.02
Hydroxychloroquine (N=96)	19 (20)	8 (10)	11 (69)	0.001

Abbreviations: PH Pulmonary Hypertension. BMI body mass index; WHO: World Health Organisation; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO diffusing capacity for carbon monoxide (CO); KCO transfer coefficient of the lung for carbon monoxide (DLCO/alveolar volume, VA): transfer coefficient of the lung for carbon monoxide, 6MW: 6-min walk distance; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; CO cardiac output; CI cardiac index; PVR: pulmonary vascular resistance, PDE phosphodiesterase inhibitor, ERA endothelin receptor antagonist, MMF mycophenolate mofetil, na not available. Data are expressed as n (%), mean (SD) or median (interquartile range), using Fisher's exact tests for parametric data, Wilcoxon rank sum for nonparametric data, Chi2 for categorical data.

Table 2. Cox proportional hazards ratios for survival in UK patients with sarcoidosis-associated pulmonary hypertension. Univariable and multivariable analysis performed, assessing the impact on survival of baseline factors. For the multivariable model, adjustments were made for age, sex, mPAP, FVC % predicted, monotherapy vs combination therapy.

	n	Unadjusted		Adjusted	
		HR [95% CI]	p value	HR [95% CI]	p value
Age	80	1.00 [0.96-1.05]	0.85	1.05 [0.96-1.14]	0.29
Sex	80	0.67 [0.31-1.48]	0.32	0.75 [0.25-2.27]	0.61
mPAP	80	1.01 [0.98-1.05]	0.42	1.02 [0.98-1.08]	0.32
PVR	65	0.99 [0.89-1.09]	0.79		
BNP	65	1.00 [0.99-1.00]	0.72		
FVC%	78	0.95 [0.92-0.98]	0.001	0.93 [0.89-0.97]	0.001
DLCO%	54	0.93 [0.87-1.00]	0.05		
KCO%	47	0.99 [0.94-1.02]	0.48		
Mono vs. combination	80	0.38 [0.15-0.96]	0.04	0.25 [0.06-1.02]	0.053

Abbreviations: BNP brain natriuretic peptide; FVC: forced vital capacity; DLCO diffusing capacity for carbon monoxide (CO); KCO transfer coefficient of the lung for carbon monoxide; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance.

also associated with fibrosis severity as measured by lung function values (predicted FVC). A trend to improved survival in this study (p=0.053) was seen in patients receiving combination PH therapy over monotherapy, however there are limitations inherent to any registry analysis, including missing data, potential overlap given the use of sequential rather than upfront combination therapy, and potential confounding of year of diagnosis. In previous case series, the use of upfront combination PH therapies improved clinical parameters (10), and, given the paucity clinical evidence in this well phenotyped patient group with poor outcomes, highlights the urgent need for well-conducted prospective studies in this population. In addition, our results highlight the need for more research to standardize care, and, to support international guidelines for best practice, the need for prospective clinical trials to determine clinical efficacy of PAH therapies in patients with SAPH.

Abbreviations: 6MWD: 6-minute walk distance; SAPH: Sarcoidosis-associated pulmonary hypertension; PH: Pulmonary hypertension; PAH: Pulmonary arterial hypertension; RV: Right ventricle; RHC: Right heart catheterization; RAP: Right atrial pressure; mPAP: Mean pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure; CO: cardiac output; CI: Cardiac index; PVR: Pulmonary vascular resistance; COPD: Chronic obstructive pulmonary disease; ILD: Interstitial lung disease; DLCO: Diffusing capacity of the lung for carbon monoxide; KCO: Transfer coefficient for carbon monoxide; ERA: Endothelin Receptor Antagonist; PDE: Phosphodiesterase; FEV1: Forced expiratory volume in 1 second; FVC: Functional vital capacity; ILD: Interstitial lung disease

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