Prostacyclin and Oral Vasodilator Therapy in Sarcoidosis-Associated Pulmonary Hypertension

A Retrospective Case Series

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BACKGROUND: It is unclear whether recent advances in pulmonary arterial hypertension therapy can be safely applied to sarcoidosis-associated pulmonary hypertension (SAPH). Evidence for prostacyclin (PG) therapy in SAPH is limited.

METHODS: We conducted a single-center, retrospective review of 46 patients with sarcoidosis, 26 of whom had SAPH. Thirteen received PG as monotherapy or in combination with oral vasodilators.

RESULTS: Follow-up right-sided heart catheterization at a mean of 12.7 months revealed improved cardiac output, cardiac index, and pulmonary vascular resistance. Functional class and N-terminal pro-brain natriuretic peptide levels also improved in patients treated with PG. No significant change in oxygen requirement was seen with vasodilator therapy initiation. At 2 years, 15 patients with SAPH survived, including eight on PG, and at 5 years, seven survived, including five on PG. Survival was significantly reduced in patients with SAPH compared with patients who had sarcoidosis without pulmonary hypertension. Multivariate analysis demonstrated that the use of PG therapy in SAPH is not associated with increased mortality.

CONCLUSIONS: Many patients with severe SAPH showed significant hemodynamic and clinical improvement on long-term IV or subcutaneous PG therapy and had survival outcomes similar to patients with moderate SAPH on oral vasodilator therapy.

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ABBREVIATIONS: DLCO = diffusing capacity of lung for carbon monoxide; FC = functional class; HR = hazard ratio; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PG = prostacyclin; PH = pulmonary hypertension; RHC = right-sided heart catheterization; SAPH = sarcoidosis-associated pulmonary hypertension; TTE = transthoracic echocardiography

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Sarcoidosis is a multisystem granulomatous disease that can affect the pulmonary interstitium, thoracic lymph nodes, airways, and pulmonary vasculature. Pulmonary hypertension (PH) is found in 5.7% to 28.3% of patients with sarcoidosis^{1,2} and is common in those with fibrotic lung disease.³ Among patients with sarcoidosis referred for lung transplantation, 73.8% have sarcoidosis-associated PH (SAPH).⁴ Compared with patients affected by sarcoidosis without PH, patients with SAPH face more functional disabilities⁴ and higher mortality.⁵

Sarcoidosis is classified among group 5 PH disorders due to multiple etiologies.⁶ Mechanisms leading to SAPH include capillary obliteration secondary to fibrosis, altered vascular mechanics due to parenchymal distortion,⁷ impingement of vasculature by enlarged

lymph nodes, granulomatous angiitis, pulmonary veno-occlusion,⁸ and left ventricular dysfunction.⁹ It is unclear whether pulmonary arterial hypertension (PAH) therapies are applicable to SAPH. Extension of PAH-specific therapy to SAPH is complicated by a heterogeneous vasodilator response in sarcoidosis.^{10,11} Evidence for the use of prostacyclin (PG) therapy in SAPH is limited.

We present the largest case series to our knowledge of patients with SAPH treated with PH-specific therapy in the United States, highlighting our experience with PG therapy. To better understand the PH-associated mortality in sarcoidosis, we also examined predictors of SAPH survival compared with non-PH sarcoidosis with similar pulmonary disease involvement.

Materials and Methods

Study Patients

We reviewed records of patients with SAPH treated at the University of Chicago from 2004 to 2014. Data were obtained with informed consent under institutional review board #13-1367.¹² Patients met standard diagnostic criteria for sarcoidosis¹³ and had a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg as measured by right-sided heart catheterization (RHC). Exclusion criteria were the following: (1) PH secondary to left-side heart failure, connective tissue disease, portal hypertension, HIV, thromboembolic disease, anorexigen use, or congenital or valvular heart disease; (2) World Health Organization functional class (FC) I or II; or (3) never received PH-specific therapy. If pulmonary capillary wedge pressure was > 15 mm Hg, the case was reviewed by physicians specializing in PH and included if PAH was the primary etiology for SAPH.

We identified patients with sarcoidosis but without PH from the University of Chicago interstitial lung disease clinic. These patients had normal

right ventricular size and function on transthoracic echocardiography (TTE) or cardiac MRI performed at the discretion of their physician as standard of care. This cohort provided informed consent under institutional review board #14163A.

Statistical Methods

Continuous variables are reported as medians with interquartile range and compared using the two-sample Wilcoxon-Mann-Whitney test. Categorical variables are reported as counts and percentages and compared using χ^2 or Fisher exact test. Paired RHC, N-terminal pro-brain natriuretic peptide (NT-proBNP) level, and oxygenation data were compared using the Wilcoxon signed rank test. Survival analysis was performed using univariate and multivariate Cox regression with unadjusted log-rank test and plotted using the Kaplan-Meier survival estimator. Survival time was defined as time from RHC in patients with PH or TTE or cardiac MRI in those without PH to death, transplant, or end of the study period. Patients were censored at the time of transplant or loss to follow-up. All data were analyzed using Stata 13 statistical software (StataCorp LP).

Results

Study Population

Thirty-two patients with SAPH were identified, and six were excluded for the following reasons: Two had PH from left-side heart failure, two were FC II, and two did not receive PH-specific therapy. Thus, 26 patients with SAPH met the inclusion criteria, of whom 13 received PG. Seven received epoprostenol, and six received treprostinil.

For the non-PH cohort, 40 patients with sarcoidosis were identified. Nine did not undergo TTE or cardiac MRI. Eleven had right ventricular dilation or dysfunction, leaving 20 patients for analysis.

Patient demographics are shown in Table 1. There were no differences in age, sex, or BMI. The median age of patients with SAPH receiving PG was 50 years, and

69% were women. Pulmonary function tests were available in 22 patients with SAPH, showing severe disease with a median diffusing capacity of lung for carbon monoxide (DLCO) of 29% predicted.

Patients with SAPH treated with PG had more severe PH than those receiving other PH-specific therapy based on RHC hemodynamic parameters. Baseline pulmonary function tests and the presence of pulmonary fibrosis were not significantly different.

Hemodynamic Outcomes

Ten patients who received PG underwent follow-up RHC at a mean time of 12.7 months after PG initiation. Cardiac output improved significantly from 3.4 L/min to 5.3 L/min ($P = .0069$) as did the cardiac index, which improved from 1.7 L/min/m² to 2.9 L/min/m² ($P = .0069$). Pulmonary vascular resistance improved

TABLE 1] Demographics

Demographic	Sarcoidosis Non-PH (n = 20)	Sarcoidosis With PH (n = 26)	P Value	SAPH Treated With PG (n = 13)	SAPH Treated With Non-PG (n = 13)	P Value
Age at sarcoidosis diagnosis, y	42 (36-52)	37 (33-46)	.13	35 (33-46)	38 (29-45)	.76
Age at PH assessment, y	49 (42-61)	50 (44-56)	.91	50 (41-56)	52 (45-55)	.86
Female sex	15 (75)	20 (77)	1.00	9 (69)	11 (85)	.64
Black American	15 (75)	22 (85)	.47	10 (77)	12 (92)	.59
BMI, kg/m ²	31 (26-37)	30 (26-34)	.57	28 (26-33)	32 (28-34)	.35
Baseline WHO FC						
III	...	20 (77)	...	7 (54)	13 (100)	.015
IV	...	6 (23)	...	6 (46)	0 (0)	...
Baseline hemodynamics by RHC						
RAP, mm Hg	...	8 (4-14)	...	12 (6-18)	5 (3-8)	.076
mPAP, mm Hg	...	46 (38-56)	...	55 (46-59)	38 (36-45)	.0012
CO, L/min	...	4.3 (3.5-5.4)	...	3.5 (2.9-3.9)	5.4 (4.4-5.8)	.0004
Cardiac index, L/min/m ²	...	2.1 (1.8-2.6)	...	1.8 (1.6-2.1)	2.5 (2.4-3.1)	.0003
PVR, mm Hg/L/min	...	8.3 (5.7-11.1)	...	11.0 (10.0-15.5)	5.7 (5.0-7.4)	.0002
Pao ₂ saturation, %	...	63 (55-68)	...	56 (51-62)	68 (63-73)	.0094
Prostanoid type						
Epoprostenol	...	7 (27)	...	7 (54)	...	...
Treprostinil	...	6 (23)	...	6 (46)	...	...
Other concurrent or previous PH therapy						
Endothelin receptor antagonist	...	12 (46)	...	5 (38)	7 (54)	.70
Phosphodiesterase type 5 inhibitor	...	20 (77)	...	8 (62)	12 (92)	.16
Calcium channel blocker	...	1 (4)	...	0 (0)	1 (8)	1.00
NT-proBNP at study entry, pg/mL	88 (47-148) ^a	1,143 (319-2,492) ^b	.0002	2,207 (1,430-2,673) ^c	457 (233-1,096) ^d	.019
Pulmonary function tests						
TLC, % predicted	83 (70-91)	68 (59-80)	.018	69 (61-77)	63 (54-84)	.59
FEV ₁ , % predicted	82 (57-92)	48 (38-59)	.0010	52 (36-66)	48 (38-58)	.58
FVC, % predicted	71 (59-81)	48 (44-64)	.0060	53 (44-68)	45 (38-64)	.47

(Continued)

TABLE 1] (continued)

Demographic	Sarcoidosis Non-PH (n = 20)	Sarcoidosis With PH (n = 26)	P Value	SAPH Treated With PG (n = 13)	SAPH Treated With Non-PG (n = 13)	P Value
FEV ₁ /FVC	78 (72-88)	72 (64-82)	.031	71 (54-82)	74 (65-82)	.65
Dlco, % predicted	76 (55-94)	29 (25-44)	.00001	29 (25-52)	30 (26-39)	.93
Pulmonary fibrosis on chest HRCT scan	7 (37) ^e	21 (84) ^f	.002	10 (77)	11 (85)	.59
Supplemental oxygen use	3 (15)	21 (81)	.0001	11 (85)	10 (77)	1.00
Prednisone therapy	7 (35)	21 (81)	.002	11 (85)	10 (77)	1.00
Steroid-sparing therapy						
Methotrexate	1 (5)	2 (8)	1.00	0 (0)	2 (16)	.48
Hydroxychloroquine	1 (5)	1 (4)	1.00	1 (8)	0 (0)	1.00
Mycophenolate mofetil	0 (0)	2 (8)	.50	1 (8)	1 (8)	1.00
Tacrolimus and azathioprine	0 (0)	1 (4)	1.00	1 (8)	0 (0)	1.00
Extrapulmonary sarcoidosis						
Cardiac	2 (10)	0 (0)	.13	0 (0)	0 (0)	1.00
Hepatic	3 (15)	2 (8)	.64	1 (8)	1 (8)	1.00
Dermatologic	6 (30)	2 (8)	.062	2 (16)	0 (0)	.24
Sinonasal	3 (15)	0 (0)	.075	0 (0)	0 (0)	1.00
Ophthalmologic	2 (10)	2 (8)	1.00	0 (0)	2 (16)	.48
Neurologic	1 (5)	1 (4)	1.00	1 (8)	0 (0)	1.00

Data are presented as median (interquartile range) or No. (%). CO = cardiac output; Dlco = diffusing capacity of lung for carbon monoxide; FC = functional class; HRCT = high-resolution CT; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PG = prostacyclin; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right-sided heart catheterization; SAPH = sarcoidosis-associated pulmonary hypertension; TLC = total lung capacity; WHO = World Health Organization.

^an = 8.

^bn = 23.

^cn = 11.

^dn = 12.

^en = 19.

^fn = 25.

TABLE 2] Response to PG Therapy by RHC

Parameter	RHC Before PG Initiation (n = 10)	Follow-up RHC on PG (n = 10)	P Value
RAP, mm Hg	11 (5-18)	4.5 (4-11)	.61
mPAP, mm Hg	55 (46-58)	52 (43-54)	.24
CO, L/min	3.4 (2.7-3.8)	5.3 (4.1-6.3)	.0069
Cardiac index, L/min/m ²	1.7 (1.5-2.1)	2.9 (2.4-3.8)	.0069
PVR, mm Hg/L/min	11.6 (10-17)	5.9 (5.6-8.2)	.037
Pao ₂ saturation, %	57 (52-60)	67 (61-77)	.17

Data are presented as median (interquartile range). See Table 1 legend for expansion of abbreviations.

from 11.6 mm Hg/L/min to 5.9 mm Hg/L/min ($P = .037$). No significant difference was seen in mPAP, pulmonary artery oxygen saturation, or right atrial pressure (Table 2). Among patients treated with PG who did not undergo follow-up RHC, one died after 11 months of possible neurosarcoidosis, one died after 6 months of unknown cause, and one died within 24 h of starting emergent PG therapy for right heart failure.

Functionality, NT-proBNP, and Oxygenation

At study entry, six patients who received PG were FC IV and seven FC III. Reassessment was available for eight patients at 1 year, and all improved or stabilized at FC II or III. By year 3 of PG therapy, seven of 13 patients survived with sustained improvement in FC (Table 3). A repeat 6-min walk test was available in three patients on PG, revealing a mean gain of 32.6 m 9 months after therapy initiation. Five patients on non-PG vasodilators with serial 6-min walk tests also showed a mean gain of 32.6 m at a mean follow-up of 4 months.

The median NT-proBNP level in patients receiving PG was 2,207 pg/mL at study entry, decreasing to 354 pg/mL at 1 year ($P = .050$) and 49 pg/mL after 3 years (Fig 1) of treatment. There was no significant difference between median oxygen supplementation before and after PG and non-PG vasodilator therapy.

Survival

Fifteen patients in the sarcoidosis cohort died, 13 of whom had SAPH. One patient with SAPH underwent lung transplantation, and one was lost to follow-up. Patients with SAPH had significantly reduced survival compared with those without PH in unadjusted log-rank analysis ($P = .0014$) (Fig 2). PH independently predicted mortality in univariate and multivariate Cox regression analysis (hazard ratio [HR], 7.06; 95% CI, 1.02-48.8; $P = .048$), adjusting for age and FVC (Table 4). Age also independently predicted mortality in multivariate analysis (HR, 1.07; 95% CI, 1.0-1.15; $P = .025$). Higher FVC was associated with improved survival in the

TABLE 3] WHO FC Change Over 3-Year Follow-up in Patients With Sarcoidosis-Associated PH Who Received PG Therapy

Patient	Study Entry	PG Initiation	Year 1 on PG	Year 2 on PG	Year 3 on PG
1	4	4	3	3	3
2	3	3	Missing	...	2
3	3	4	Died	...	...
4	4	3	3	2	Died
5	4	4	3	2	3
6	3	3	Died	...	...
7	4	4	3	3	3
8	4	4	Died	...	...
9	3	3	3	Died	...
10	3	4	Died	...	...
11	3	3	3	3	3
12	4	4	2	2	3
13	3	3	3	2	2

See Table 1 legend for expansion of abbreviations.

Figure 1 – NT-proBNP levels declined in patients with sarcoidosis-associated PH on prostacyclin therapy. NT-proBNP = N-terminal pro-brain natriuretic peptide. PH = pulmonary hypertension.

multivariate model but did not reach statistical significance (HR, 0.95; 95% CI, 0.91-1.0; $P = .06$).

No significant difference in survival was found between patients treated with PG and those receiving other PH-specific therapy ($P = .71$) (Fig 3). PG therapy was associated with a nonsignificant reduction in mortality risk (HR, 0.2; 95% CI, 0.07-7.46; $P = .4$) in a multivariate Cox regression model adjusting for mPAP and FVC (Table 5). FVC was the only significant predictor of mortality among patients with SAPH in this multivariate analysis.

FVC and DLCO independently predicted mortality in univariate analysis, but only FVC remained significant in multivariate models containing both variables. Therefore, DLCO was excluded from the final models presented in Tables 4 and 5.

Figure 2 – Patients with sarcoidosis-associated PH had decreased survival. See Figure 1 legend for expansion of abbreviation.

Discussion

To our knowledge, this series is the largest published to date of patients with SAPH treated with IV or subcutaneous PG therapy, the largest of patients with World Health Organization FC IV SAPH in the United States, and the first to report long-term use of treprostinil in SAPH. The patient population in this study comprised predominantly of self-identified black American women is an underreported demographic in the SAPH literature, despite the increased prevalence of sarcoidosis in black Americans.

We found that patients with SAPH have significantly increased mortality compared with patients who have sarcoidosis without PH. After adjusting for age and FVC, PH remained a significant predictor of mortality. We did not find survival differences between patients with SAPH treated with PG and those receiving other PH-specific therapies, suggesting that PG may be a therapeutic option for these patients with severe disease.

Literature regarding SAPH management is largely based on medications studied rigorously in group 1 PAH. PH-specific therapies have been reported in SAPH, including sildenafil,^{11,14-16} ambrisentan,¹⁷ and bosentan.¹⁸ Studies have described the use of inhaled nitric oxide,¹⁰ inhaled iloprost,¹⁹ and IV epoprostenol.^{10,20}

In the current study, nine of 13 patients with SAPH treated with PG were alive at 1 year, and eight showed an improvement in FC. Among those who survived and remained on long-term PG therapy, we found significant improvements in hemodynamics, FC, and NT-proBNP levels.

The current results differ from Fisher et al,²⁰ who reported FC improvement in all five patients with SAPH treated with long-term epoprostenol. No significant differences were found in baseline mPAP between patients receiving PG in the present study and those in the Fisher et al study, suggesting that PH severity in these cohorts is similar. Barnett et al¹⁵ reported treatment of 22 patients with SAPH with various PH-specific therapies. One patient received IV epoprostenol, and five received inhaled iloprost in combination with sildenafil or bosentan. Survival for the current study patients with SAPH was worse than that in the Barnett et al cohort because fewer patients underwent lung transplantation.

Like previous studies of SAPH, the current sample size was limited. A meta-analysis of 56 patients from five studies found that mPAP, cardiac output, and pulmonary vascular resistance improved in patients with

TABLE 4] Variables Predicting Survival in Patients With Sarcoidosis

Characteristic	Log-Rank <i>P</i> Value	Unadjusted (n = 46) ^a			Adjusted (n = 42) ^b		
		HR	95% CI	<i>P</i> Value	HR	95% CI	<i>P</i> Value
PH	.001	7.92	1.78-35.3	.007	7.06	1.02-48.8	.048
Age	...	1.03	0.99-1.08	.13	1.07	1.0-1.15	.025
FVC, % predicted	...	0.95	0.92-0.98	.003	0.95	0.91-1.0	.06
DLco, % predicted	...	0.94	0.90-0.98	.001	...	...	...
Male sex	.24	1.91	0.64-5.7	.25	...	...	...
Corticosteroid therapy	.17	2.21	0.7-6.99	.18	...	...	...

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

^aException for number of patients: FVC, n = 42; DLco, n = 37.

^bAdjusted for age and FVC % predicted.

Figure 3 – Patients with severe sarcoidosis-associated PH on prostacyclin therapy had no survival difference compared with patients who had moderate PH treated by oral vasodilators. See Figure 1 legend for expansion of abbreviation.

SAPH receiving PH-specific therapy.¹⁶ The current analysis was retrospective. Expert clinicians made therapeutic decisions case by case, and treatment choice was not blinded.

Conclusions

PG therapy and oral vasodilators were well tolerated by many patients with SAPH in this cohort, with evidence for clinical and hemodynamic improvement. In multivariate analysis adjusting for mPAP, FVC, and PG therapy use, only FVC significantly predicted mortality for patients with SAPH. IV or subcutaneous PG was not associated with increased mortality and may be considered a potential treatment in severe SAPH. Further studies are needed to determine how PG therapy affects mortality and long-term outcomes.

TABLE 5] Variables Predicting Survival in Patients With Sarcoidosis-Associated PH

Characteristic	Log-Rank <i>P</i> Value	Unadjusted (n = 26) ^a			Adjusted (n = 22) ^b		
		HR	95% CI	<i>P</i> Value	HR	95% CI	<i>P</i> Value
Prostacyclin therapy	.71	1.24	0.4-3.82	.7	0.23	0.07-7.46	.4
mPAP	...	1.03	0.99-1.08	.16	1.1	0.95-1.29	.18
FVC, % predicted	...	0.92	0.85-0.99	.02	0.92	0.85-0.99	.02
DLco, % predicted	...	0.93	0.87-0.99	.03	...	...	...
Age	...	1.07	1-1.15	.06	...	...	...
Male sex	.23	2.06	0.62-6.86	.24	...	...	...
Corticosteroid therapy	.85	0.86	0.19-3.99	.85	...	...	...

See Table 1 and 4 legends for expansion of abbreviations.

^aException for number of patients: FVC, n = 22; DLco, n = 18.

^bAdjusted for mPAP and FVC % predicted.

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