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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 disabilities[4] 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 sarcoidosis[13] and had a mean pulmonary artery pressure (mPAP) $\geq$ 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/m^2 to 2.9 L/min/m^2 ($P = .0069$). Pulmonary vascular resistance improved