Sarcoidosis-Associated Pulmonary Hypertension*

Outcome With Long-term Epoprostenol Treatment

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Rationale: **Pulmonary hypertension is a known complication of sarcoidosis and is associated with increased mortality. Little is known about the outcome of sarcoidosis-associated pulmonary hypertension, including response to treatment.**

Objective: **To determine the characteristics and outcome of patients with sarcoidosis-associated pulmonary hypertension treated with IV epoprostenol.**

Design: **Retrospective chart review of all cases of pulmonary hypertension with a concomitant diagnosis of sarcoidosis evaluated in the Boston University Pulmonary Hypertension Center from 2000 to 2004.**

Measurements: **Data collected included patient demographics, sarcoidosis stage, pulmonary function, echocardiography results, treatment, baseline and posttreatment hemodynamic measurements, and clinical outcome.**

Results: **Eight patients were identified; four of the patients had stage IV pulmonary sarcoidosis. Pulmonary function test results were notable for severe diffusion impairment (mean diffusion capacity of the lung for carbon monoxide, 30% of predicted), with only mild-to-moderate restrictive physiology (mean FVC, 59% of predicted). Seventy-five percent of patients required supplemental oxygen at the time of presentation. All patients had moderate or severe pulmonary hypertension and were New York Heart Association (NYHA)/World Health Organization (WHO) class III or IV. A vasodilator trial with epoprostenol was performed in seven of the eight patients; six of the seven patients had a significant hemodynamic response (> 25% reduction in pulmonary vascular resistance). All but one of the responders (five of six patients) continued on therapy. Average clinical improvement was one to two NYHA/WHO classes at a mean follow-up of 29 months (range, 15 to 49 months).**

Conclusions: **In patients with sarcoidosis-associated pulmonary hypertension, the severity of pulmonary vascular disease occurs out of proportion to lung function abnormalities. The majority of our patients responded to epoprostenol; survival may be improved in this group.**

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Key words: granulomatous disease; prostanoid therapy; pulmonary circulation; pulmonary vascular disease

Abbreviations: iNO = inhaled nitric oxide; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RHC = right-heart catheterization; SVR = systemic vascular resistance; WHO = World Health Organization

Pulmonary hypertension is a well-described complication of sarcoidosis. When all stages of sarcoidosis are considered, studies[1,2] have demonstrated elevated pulmonary artery pressure (PAP) in 6 to 23% of patients at rest, and as many as 43% with exertion.[2] The increase in PAP is typically mild to moderate but can be severe.[3–8] Advanced sarcoidosis is more commonly complicated by pulmonary hypertension. Shorr and coworkers[9] recently reviewed right-heart catheterization (RHC) data from 363 sarcoidosis patients awaiting lung transplantation and found that 73.8% had pulmonary hypertension. Furthermore, the presence of pulmonary hypertension has been shown to be an independent risk factor of mortality from sarcoidosis in patients awaiting lung transplantation.[10]

Treatment of pulmonary arterial hypertension associated with sarcoidosis is controversial and based

on limited data. While some case reports[7,11,12] describe regression of pulmonary hypertension with steroid treatment, others[3,5,13] describe no improvement or even worsening despite steroid therapy. Recently, Nunes et al[14] reported a series of 22 patients with sarcoidosis-associated pulmonary hypertension; of the 10 patients treated with corticosteroids in this series, 3 patients had documented decreases in systolic PAP in response to steroids. Reports of acute vasoreactivity in response to epoprostenol suggest a role for long-term treatment with vasodilators in the management of sarcoidosis-associated pulmonary hypertension.[4,15,16] However, the safety and long-term efficacy of IV epoprostenol in patients with sarcoidosis-associated pulmonary hypertension is not known.

In the current report, we describe the acute response to epoprostenol and the outcome with long-term administration of epoprostenol in patients with sarcoidosis-associated pulmonary hypertension. Of note, this study was not designed to evaluate the prevalence of pulmonary hypertension in patients with sarcoidosis, but to describe the response of patients with sarcoidosis-associated pulmonary hypertension to epoprostenol treatment. To our knowledge, this is the largest group of patients with sarcoid-associated pulmonary hypertension treated with long-term epoprostenol therapy.

Materials and Methods

Design and Data Collection

In accordance with the protocol approved by the Institutional Review Board, we retrospectively reviewed all cases of pulmonary hypertension evaluated in the Boston University Pulmonary Hypertension Center between January 2000 and October 2004 and identified patients with a concurrent diagnosis of sarcoidosis. Data collected included patient demographics, sarcoidosis stage, treatment, pulmonary function, echocardiography results, baseline and posttreatment hemodynamics, complications of vasodilator therapy, and long-term clinical outcome.

Patients

All patients with known diagnoses of both sarcoidosis and pulmonary hypertension were identified. The diagnosis of sarcoidosis was confirmed by review of the medical record, including compatible historical information and/or pathology findings. Patients were classified as having sarcoidosis-associated pulmonary hypertension if they had a mean PAP (mPAP) $\geq$ 25 mm Hg at RHC and did not have evidence of connective tissue disease, portal hypertension, elevated pulmonary capillary wedge pressure, congenital or valvular heart disease, HIV disease, history of anorexigen use, thromboembolic disease, or obstructive sleep apnea.

In one patient, the diagnosis of sarcoidosis-associated pulmonary hypertension was based on Doppler echocardiographic findings of pulmonary hypertension (right ventricular dilation, hypokinesis, and estimated pulmonary artery systolic pressure $>$ 40 mm Hg in the setting of normal left ventricular size and function). This patient, however, died prior to invasive confirmation of pulmonary arterial hypertension and vasodilator challenge and is excluded from the analysis below.

Acute Vasodilator Testing

Informed consent for RHC was obtained from all patients. The patients were admitted to the medical ICU at Boston Medical Center for insertion of a pulmonary artery catheter (right internal jugular or left subclavian vein approach). After insertion, baseline hemodynamic measures were obtained. Per protocol, IV epoprostenol was then initiated at 2 ng/kg/min, and increased by 2 ng/kg/min every 15 min, until signs or symptoms of systemic toxicity (headache, jaw pain, nausea, vomiting, flushing, or systemic hypotension) developed. Hemodynamic measurements were performed prior to each incremental dose increase.

Long-term Vasodilator Treatment

Long-term IV epoprostenol therapy was administered via a centrally inserted tunneled catheter immediately following the vasoreactivity testing. No patient was a candidate for oral calcium-channel blockers because all patients had severe pulmonary hypertension based on pulmonary vascular resistance (PVR) and New York Heart Association (NYHA)/World Health Organization (WHO) functional class. Dose adjustments were made as dictated by patient symptoms (especially exertional dyspnea) and clinical status. Patients were treated with supplemental oxygen as required to maintain oxygen saturation $\geq$ 90%. All patients treated with long-term vasodilators also received anticoagulation with warfarin to a international normalized ratio of 2 to 3.

Immunosuppressive Therapy

Corticosteroid or immunosuppressive therapy was initiated or continued based on standard indications for treatment of sarcoidosis (*ie*, hypercalcemia, pulmonary, ocular, or CNS involvement).

Statistical Analysis

Our primary outcome measure was the acute percentage change in PVR, with change in right atrial pressure and cardiac output as secondary outcomes. The Wilcoxon signed-rank test was used to assess the significance of the change with an α level of $p = 0.05$.

Results

Patients

Eight patients with sarcoidosis-associated pulmonary hypertension were identified (Table 1). In 75% of

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