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Treatment of newly diagnosed sarcoid-associated pulmonary hypertension with ambrisentan and tadalafil combination therapy

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Abstract. Sarcoid Associated Pulmonary Hypertension (SAPH) is a common complication of sarcoidosis and is associated with poor prognosis. SAPH can be due to multiple synergistic mechanisms and current therapeutic strategies treat systemic sarcoidosis and pulmonary hypertension separately. Several studies have been performed to develop an effective therapy for SAPH but have been met with mixed results. The AMBITION trial successfully treated incident patients with pulmonary arterial hypertension (PAH) with the upfront combination of ambrisentan and tadalafil; however combination therapy has not yet been studied in patients with SAPH. Here we report a cohort of patients with newly diagnosed SAPH who were treated with upfront combination therapy per the AMBITION study protocol. We report three subjects with newly diagnosed SAPH who were treated with combination ambrisentan and tadalafil. Baseline hemodynamics were compared with those from surveillance right heart catheterization while on therapy. Mean follow up period was 17 months. Each subject demonstrated clinical and hemodynamic improvement with combination therapy. This series is the first to evaluate upfront combination ambrisentan and tadalafil therapy for treatment of newly diagnosed SAPH. Despite the impressive clinical and hemodynamic improvement, the study is limited by its small size and retrospective nature. While these initial results are promising, further work is needed to fully evaluate this regimen for treatment of SAPH. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 234-238)*

Key words: Sarcoid associated pulmonary hypertension, sarcoidosis, pulmonary hypertension, Ambition Protocol, tadalafil, ambrisentan.

Introduction

Sarcoid Associated Pulmonary Hypertension (SAPH) is a well-known complication of sarcoidosis. SAPH is thought to develop as a result of complex interactions between sarcoid-associated inflammatory processes in both the lung parenchyma and the pulmonary vasculature. Mechanisms by which sarcoid disease can induce pulmonary hypertension include: hypoxia, pulmonary artery vasculitis, sarcoid associated heart failure, fibrotic destruction of pulmonary vasculature, occlusion of pulmonary vasculature by granulomatous tissue, and sarcoid-induced hepatic disease and subsequent portopulmonary hypertension[1]. Historically, SAPH has been difficult to study because any of these mechanisms can contribute to the development of SAPH[2]. While the epidemiology of SAPH has been the subject of several recent studies, its exact incidence remains unknown. In the largest cohorts of patients with known sarcoidosis who were screened for Pulmonary Hypertension (PH) by echocardiography SAPH was observed in 3-50%[3, 4, 5, 6]. In studies using right heart catheterization, 49-73% of patients with known sarcoidosis were diagnosed with SAPH[7, 8]. This broad range is likely due, in part to the heterogeneity of the sarcoid population and

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the varying severity of the underlying sarcoidosis. Yet, the presence of SAPH confers a poorer prognosis compared to sarcoidosis alone[3, 9, 10, 11].

Treatment of SAPH has focused on optimizing treatment of the underlying sarcoidosis and management of the PH as distinct issues. Studies specifically evaluating the effect of treating the sarcoidosis with immunomodulatory therapy have demonstrated mixed results on pulmonary hemodynamics[10, 12, 13, 14]. Use of pulmonary vasodilators approved for treatment of Pulmonary Arterial Hypertension (PAH) in patients with SAPH has been hampered by a lack of robust studies evaluating such treatment in this population. What is known is based on small studies[15]. For example, prostanoids have been effective vasodilators in SAPH[16, 17] whether administered by the inhaled or intravenous route[18, 19, 20]. In addition, endothelin receptor antagonists (bosentan) and phosphodiesterase-5 inhibitors (sildenafil) have improved SAPH in some patients[21, 22, 23]

The benefits of upfront combination therapy have recently been established in patients with newly diagnosed group 1 PH (PAH); AMBITION was the first randomized controlled trial to demonstrate improvement in outcomes with the upfront combination of ambrisentan and tadalafil in the treatment of newly diagnosed PAH[24]. Previously, ambrisentan mono-therapy had demonstrated improvement in exercise capacity and hemodynamics in patients with PAH. Likewise, tadalafil, as either monotherapy or add on therapy, also improved hemodynamics, six minute walk test, and time to clinical worsening[25, 26]. In patients with SAPH treatment with either of these agents as monotherapy has led to variable results. Ambrisentan monotherapy did demonstrate improvement in functional class in one study[27]. Likewise, tadalafil monotherapy has demonstrated equivocal results in this patients population[28]. However, there are no studies that have evaluated combination therapy in patients with newly diagnosed SAPH.

In the current report, we describe a series of newly diagnosed SAPH patients treated with the upfront combination of ambrisentan and tadalafil (AMBITION protocol)[24].

Design and Data Collection

We conducted a retrospective review of all patients with SAPH and identified those treated with the combination of ambrisentan and tadalafil (AMBITION protocol) in accordance with a protocol approved by the Boston University Institutional Review Board. For each case, we collected patient demographics, stage of sarcoidosis, treatment for sarcoidosis, pulmonary function testing, echocardiography, baseline and post-treatment hemodynamics, complications of therapy, and clinical outcome.

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 SAPH if they had a mean pulmonary arterial pressure (mPAP) > 25 mm Hg (Patients were diagnosed and treated under the previous PH guidelines and not under the currently proposed definition[24, 29]) by right heart catheterization (RHC) with PAOP < 15 mmHg and PVR > 3 WU. None of the patients included in this report, had evidence of any of the following: connective tissue disease, portal hypertension, congenital or valvular heart disease, HIV infection, history of anorexigen or methamphetamine use, or thromboembolic disease.

Treatment Protocol

Patients were treated in accordance with the AMBITION trial protocol. Daily ambrisentan and tadalafil were initiated following diagnostic RHC with goal of 10 mg and 40 mg daily, respectively. Dose adjustments were made as dictated by patient symptoms and clinical status. Patients were treated with supplemental oxygen as required to maintain oxygen saturation ≥90%. Patients underwent surveillance RHC to assess response to treatment as clinically indicated.

Because of its small size, this series was not powered for statistical analysis.

Results

This case series contains 3 subjects with newly diagnosed SAPH who were treated with the AMBITION protocol, with a mean follow-up of 17 months. All subjects tolerated full dose ambrisentan and tadalafil with no significant side effects. Surveillance right heart catheterization (mean interval 12 months) demonstrated improvement in hemodynamics in each patient: mPAP 40 ± 10 baseline vs 24 ± 5 mmHg post treatment, CO 3.8 ± 1.9 baseline vs 7 ± 2 L/min post treatment, PVR 12.6 ± 12.4 baseline vs 2.4 ± 0.8 WU post treatment. In addition to hemodynamic

improvement, there was also improvement in NYHA functional class from FC III at baseline to FC II post treatment and 6 minute walk distance from 305 ± 58m baseline to 427 ± 86m post treatment.

Case Descriptions:

Patient 1 is a Caucasian male with history of hypertension and distant smoking history. He was diagnosed with lung biopsy proven Scadding stage 4 sarcoidosis at age 44. He was initially managed with steroids, but two years later transitioned to hydroxychloroquine and minocycline because of disease progression. Seven years later, because of further progression, minocycline was stopped and methotrexate started with improvement in symptoms. He later developed a spontaneous pneumothorax with persistent air leak, ultimately treated by lobectomy.

At age 56, because of progressive DOE, hypoxia, and decline in lung function, he was evaluated for pulmonary hypertension; right heart catheterization demonstrated SAPH. Tadalafil and ambrisentan were started per AMBITION protocol. There were no side effects with tadalafil, but ambrisentan caused fluid retention that responded to diuretics. This treatment resulted in improved symptoms, exercise tolerance and hemodynamics. Eighteen months later he again noted progressive DOE, worsening hypoxia, and diminished exercise tolerance. Imaging demonstrated progressive fibrotic lung disease and surveillance right heart catheterization demonstrated worsening hemodynamics. Because of these findings, he eventually underwent bilateral lung transplant and is currently alive and well.

Patient 2 is a 74 year old female with history of spinal stenosis, hypothyroidism, and Scadding stage 4 sarcoidosis. Initially diagnosed at age 63 because of uveitis and arthralgia, she later developed hypercalcemia, chronic lymphopenia, and palpitations associated with recurrent supraventricular tachycardia. Sarcoidosis was diagnosed by mediastinal biopsy. She was initially treated with prednisone for two years prior to initiation of methotrexate as a steroid sparing agent. She was stable on this regimen for ~8 years; then developed worsening pulmonary disease and was transitioned to infliximab.

Because of progressive dyspnea, limiting activities of daily living, and worsening hypoxia, despite stable lung disease, she underwent right heart catheterization that demonstrated severe SAPH. She was treated with tadalafil and ambrisentan per the AMBITION protocol without side effects. With this regimen, she had dramatic improvement in symptoms, clinical status and hemodynamics. Unfortunately, twelve months later, she died from urosepsis.

Patient 3 is a 56 year old male, with history of hypertension, severe obstructive sleep apnea treated with BiPAP, type 2 diabetes, distant 33 pack/year smoking history, and Scadding stage 4 sarcoidosis. He was diagnosed with sarcoidosis in 2004 by transbronchial biopsy and treated with prednisone for several years. The sarcoidosis was difficult to control despite multiple regimens, including methotrexate, azathioprine, and infliximab; it was eventually controlled with a combination of methotrexate, adalimumab, and doxycycline.

Because of progressive dyspnea and stable lung disease, he underwent right heart catheterization that demonstrated SAPH. He was treated with tadalafil and ambrisentan per AMBITION protocol without side effects and with improvement in symptoms, clinical status, and hemodynamics. With advancing fibrotic lung disease his symptoms have again progressed and he is awaiting lung transplantation.

Discussion

In the current series of patients with biopsy proven sarcoidosis subsequently diagnosed with SAPH by right heart catheterization, we report the initial experience with upfront treatment with ambrisentan and tadalafil per the AMBITION protocol. Despite previous studies showing equivocal response to ambrisentan and tadalafil as monotherapy in patients with SAPH, these three patients responded to combination therapy with improvement in clinical status, functional class and hemodynamics. Moreover, this regimen was well-tolerated with minimal side effects.

The prospect that patients with newly diagnosed SAPH might receive significant benefit from upfront combination therapy is potentially important. The initial response to therapy seen in this small series is highly encouraging, especially since patients with a significant burden of fibrotic disease (Scadding stage 4) tend to respond poorly to vasodilator therapy. Clearly, additional studies are warranted to

investigate the effects of combination therapy in a larger cohort of patients with SAPH.

While it is difficult to generalize the results from three patients, two (patients 1 and 3) had a significant response to therapy initially, but later had progression of symptoms which was attributed to worsening fibrotic lung disease. This does suggest that combination therapy might not have long-term durability in patients suffering from progressive fibrotic disease and that these patients should be closely monitored for clinical worsening. However, the initial and extended improvement suggests that combination therapy might: 1) provide symptomatic relief and/or improvement in these patients; 2) allow time for more aggressive treatment of the advancing fibrosis; and/or 3) allow more time to evaluate the patient for lung transplantation and/or possibly delay the need for it.

The current study is limited by its small size, retrospective nature, and lack of randomization. Moreover, it was not adequately powered to detect statistically significant treatment effect changes. Conclusions: We report a cohort of three patients with biopsy proven sarcoidosis subsequently diagnosed with SAPH by right heart catheterization. Each patient was treated with an upfront combination of tadalafil and ambrisentan in accordance with the AMBITION protocol. All patients demonstrated marked improvement in hemodynamics, symptoms, and 6-minute walk distance. Although these initial results are encouraging, especially since all patients had Scadding stage 4 disease, additional studies are needed to evaluate the effect of combination therapy in patients with SAPH.

Table 2: Hemodynamics at initial diagnosis (Baseline) and after treatment (mean followup catheterization 12 months). Hemodynamic measurements were obtained by right heart catheterization at baseline (diagnosis of SAPH) and during treatment

Table 1: Patient Characteristics

	Patient 1	**Patient 2**	**Patient 3**
Age	57	73	57
Sex	Male	Female	Male
Race	Caucasian	Caucasian	Caucasian
BMI	23.4	21.8	30.1
Scadding Stage	4	4	4
Sarcoid Treatment	Methotrexate	Infliximab	Combination
Pulmonary Function Tests			
FVC L (% Pred)	2.7 (59)	1.52 (49)	2.63 (57)
FEV1 L (%Pred)	1.49 (43)	0.61 (26)	1.58 (45)
FEV1/FVC	55	40	60
DLCO mL/ mmHg/min (% Pred)	10.5 (44)	4.85 (23)	11.4 (44)
Echocardiogram			
EF (%)	60	73	58
PASP (mmHg)	47	72	NA
Right Ventricle Size	Normal	Normal	Normal
Right Ventricle Hypertrophy	No	Yes	Yes

Table 2. Patient Hemodynamics and Functional Capacity

	Baseline				**Treatment**			
	Patient 1	**Patient 2**	**Patient 3**	**Avg**	**Patient 1**	**Patient 2**	**Patient 3**	**Avg**
RV sys (mmHg)	49	58	41	49 ± 9	36	38	38	37 ± 1
RA dia (mmHg)	1	5	3	3 ± 2	0	0	0	0 ± 0
PAP sys (mmHg)	54	62	40	52 ± 11	40	40	39	40 ± 1
PAP dia (mmHg)	31	31	23	28 ± 5	23	13	6	14 ± 9
mPAP (mmHg)	40	50	31	40 ± 10	29	23	20	24 ± 5
PCWP (mmHg)	4	7	13	8 ± 5	11	5	6	7 ± 3
CO Fick (L/min)	4.84	1.61	4.86	3.8 ± 1.9	5.53	8.23	8.5	7 ± 2
CI Fick (L/min/m^2)	2.48	1.96	2.29	2.2 ± 0.3	2.97	4.9	4.04	4 ± 1
PVR Fick (WU)	7.4	26.7	3.7	12.6 ± 12.4	3.2	2.3	1.7	2.4 ± 0.8
NYHA FC	2	2	2	2	3	3	3	3
6 Min walk (M)	365	250	300	305 ± 58	450	500	332	427 ± 86

with tadalafil and ambrisentan (Treatment). RV (right ventricle), PAP (pulmonary artery pressure), mPAP (mean PAP), PCWP (pulmonary capillary wedge pressure), CO Fick (cardiac output via Fick's principle, CI cardiac index), PVR (pulmonary vascular resistance), NHYA FC (New York Heart Association Functional Class). mPAP improved from 40 ± 10 mmHg to 24 ± 5 mmHg, CI improved from 2.2 ± 0.3 to 4.0 ± 1.0 L/min/m2. The study was not powered for statistical analysis.

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