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Inhaled iloprost for sarcoidosis associated pulmonary hypertension

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Abstract. *Rationale:* Patients with sarcoidosis associated pulmonary hypertension (SAPH) have responded to systemic prostacyclin therapy. *Objectives:* To determine the rate of response to inhaled prostacyclin, iloprost, in SAPH. *Methods:* Sarcoidosis patients with pulmonary hypertension and no evidence for left ventricular dysfunction were enrolled in an open label, prospective study. Patients underwent right heart catheterization and six minute walk (6MW) test. Quality of life was evaluated using several instruments, including the Saint George Respiratory Questionnaire (SGRQ). Patients received 5 mcg of inhaled iloprost every 2-3 hours while awake. After four months of therapy, patients underwent repeat cardiac catheterization, 6 MW test, and completed quality of life questionnaires. *Measurements and Main Results:* Of the 22 patients enrolled, 15 completed all 16 weeks of therapy. The most common reasons for study discontinuation included drug associated cough (3 patients) and compliance with the prescribed number of treatments per day (2 patients). Six patients experienced a 20% or greater decrease in pulmonary vascular resistance (PVR) from baseline with five of these six patients also showing ≥ 5 mm Hg reduction in PA mean. Although three patients improved the 6MW distance by at least 30 meters, only one had a decrease in PVR. At 16 weeks a significant decrease was reported in the SGRQ activity score (p=0.0273), with seven patients having a 4 point or greater decrease. *Conclusion:* Inhaled iloprost as monotherapy was associated with an improvement in pulmonary hemodynamics and quality of life as assessed by the SGRQ activity score in some sarcoidosis patients with SAPH. *(Sarcoidosis Vasc Diffuse Lung Dis 2009; 26: 110-120)*

Key words: pulmonary hypertension, prostacyclins, stage 4 sarcoidosis

Introduction

Pulmonary hypertension is a recognized complication of sarcoidosis (1-3). The etiology of pulmonary hypertension is multifactorial, including vascular distortion from pulmonary fibrosis, hypoxemia from parenchymal lung disease, granulomatous involvement of the pulmonary vasculature, compression of vasculature from thoracic adenopathy, and pulmonary venous hypertension from left ventricular diastolic dysfunction (4, 5). According to the World Health Organization (WHO) classification system, sarcoidosis associated pulmonary hypertension (SAPH) is placed in the miscellaneous (Class V) category of pulmonary hypertension (6).

Several authors have reported successful treatment of SAPH. Many of these have been small case series (1, 7-9). Although chronic intravenous prosta-

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cyclin therapy is efficacious for some patients with SAPH (1, 7, 8), inhaled prostacyclin was not beneficial for one patient with advanced pulmonary sarcoidosis (5). In one series of 22 patients treated with various regimens, inhaled iloprost was used in four patients (10). In that series, all patients on iloprost were on other agents, so the benefit of iloprost was not clear.

While survival remains the most important end point of vasodilatory therapy, several surrogate markers have been proposed (11). These include six minute walk distance and hemodynamic changes. For sarcoidosis patients, pulmonary hypertension is one of several factors that influences six minute walk distance (12). In two studies reporting on the effect of vasodilator therapy for SAPH, one could not demonstrate any improvement in 6MWD (9), while the other found a >10% increase in 6MWD in only half of their patients (10). Both of these studies demonstrated a significant improvement in the hemodynamics in their patients (9, 10). However, both of these studies were retrospective studies and patients were reevaluated at variable time points after the initiation of therapy (13). In one study, patients received several different regimens, including a third on combination therapy (10).

The current report is the largest study to date of a single agent for SAPH. In addition, it was a prospective study, with patients reevaluated at set time points after initiation of therapy. This was a pilot study designed to allow us to determine the effect of inhaled iloprost on SAPH, including its effect on hemodynamics, 6MWD, and quality of life.

Methods

This study was conducted at the University of Cincinnati Medical Center and the Medical University of South Carolina in patients with sarcoidosis defined by current guidelines (14). Pulmonary arterial hypertension was confirmed by right heart catheterization in all patients with a pulmonary artery (PA) mean pressure of greater than 25 mmHg at rest except in one patient who had a normal PA pressure at rest which increased to greater than 30 mmHg with exercise without an increase in the pulmonary wedge pressure. All patients had left ventricular filling pressures determined by the pulmonary artery occluding pressure or left ventricular end diastolic pressures of less than 15 mm Hg. Patients were excluded for receiving any pulmonary artery hypertension specific therapy within three months of study entry. Although patients could receive systemic therapy for sarcoidosis, all patients were required to be on stable doses for at least three months prior to entry.

After meeting the inclusion and exclusion criteria and providing written informed consent of the protocol registered at ClinTrials.gov identifier NCT00403650, patients underwent initial evaluation. This included performing spirometry and a 6 MW test using a previously described protocol (12). Patients were walked on their usual oxygen levels that they used with exercise. This could be modified during the course of the study if patients were noted to become more hypoxic (saturation less than 90%) during exercise. They also completed quality of life questionnaires which included the short form 36 (SF-36), Saint George Respiratory Questionnaire (SGRQ) (15), the Sarcoidosis Health Questionnaire (SHQ) (16), and the Fatigue Assessment Scale (FAS) (17). Normal values for spirometry were calculated using a standard algorithm that is race specific (18). Chest roentgenograms performed within the past year were staged using the Scadding staging classification (19).

All patients received inhaled iloprost via a dedicated nebulizer as per the manufacturer's instructions (20). Patients were treated with 2.5 mcg iloprost delivered by the I-neb, a third generation Adaptive Aerosol Delivery (AAD) device (Phillips Respironics, Murrysville, PA). After initial inhalation, patients were monitored for two hours and then given a second treatment of iloprost using a dose of 5 mcg. Because all patients tolerated the higher dose, subsequent dosing was 5 mcg every 2-3 hours while awake. Patients were seen monthly to review symptoms and complete a toxicity questionnaire regarding drug cough and nausea. Cough and nausea were scored on a four point Likert scale with severity scored from mild (level 1) to terrible (level 4) and frequency scored from mild (level 1) to all the time (level 4). In addition, patients were queried about any other adverse events during the prior month. At each visit, patients were asked to repeat the 6MW distance after an iloprost treatment. Unused vials of drug were returned and counted at each visit to assess compliance.

At weeks 8 and 16, patients repeated the spirometry testing within 30 minutes of an inhaled iloprost treatment. At week 16, patients had spirometry, completed all the quality of life questionnaires, and underwent repeat right heart catheterization to determine pulmonary hemodynamics following drug administration.

The prespecified primary endpoint of the study was the change in the 6MW distance, and prespecified secondary endpoints including changes in pulmonary artery hemodynamics (mean pulmonary artery pressure and pulmonary vascular resistance), forced vital capacity, and quality of life as estimated by the SGRQ, SHQ, SF-36, and FAS. We also prospectively captured possible drug toxicity, including changes in the Likert scale for cough and nausea. Quality of life questionnaires were compared between the beginning and end of the study. Some patients did not answer all the questions of the quality of life questionnaires. In those cases, the results of the questionnaires were dropped from analysis. Comparisons were made between baseline and after therapy using the Mann Whitney U test and Wilcoxan rank paired test. Statistics were calculated using Medcalc statistical software (Frank Schoonjans, Mariakerke, Belgium).

Results

Figure 1 shows the outcome of the 22 patients enrolled in the trial and the 18 patients screened but who did not participate in the study. Of the 22 patients enrolled into the study, fifteen (68%) completed 16 weeks of therapy and underwent follow up right heart catheterization. Table 1 summarizes the patient demographics, pulmonary characteristics, and initial hemodynamic values of the 22 patients enrolled into the trial, and the fifteen patients who completed all 16 weeks of therapy. No differences were identified in the demographic or pulmonary characteristics for those enrolled into the study compared to those who completed the entire study. Patients were diagnosed with sarcoidosis for 1-62 years

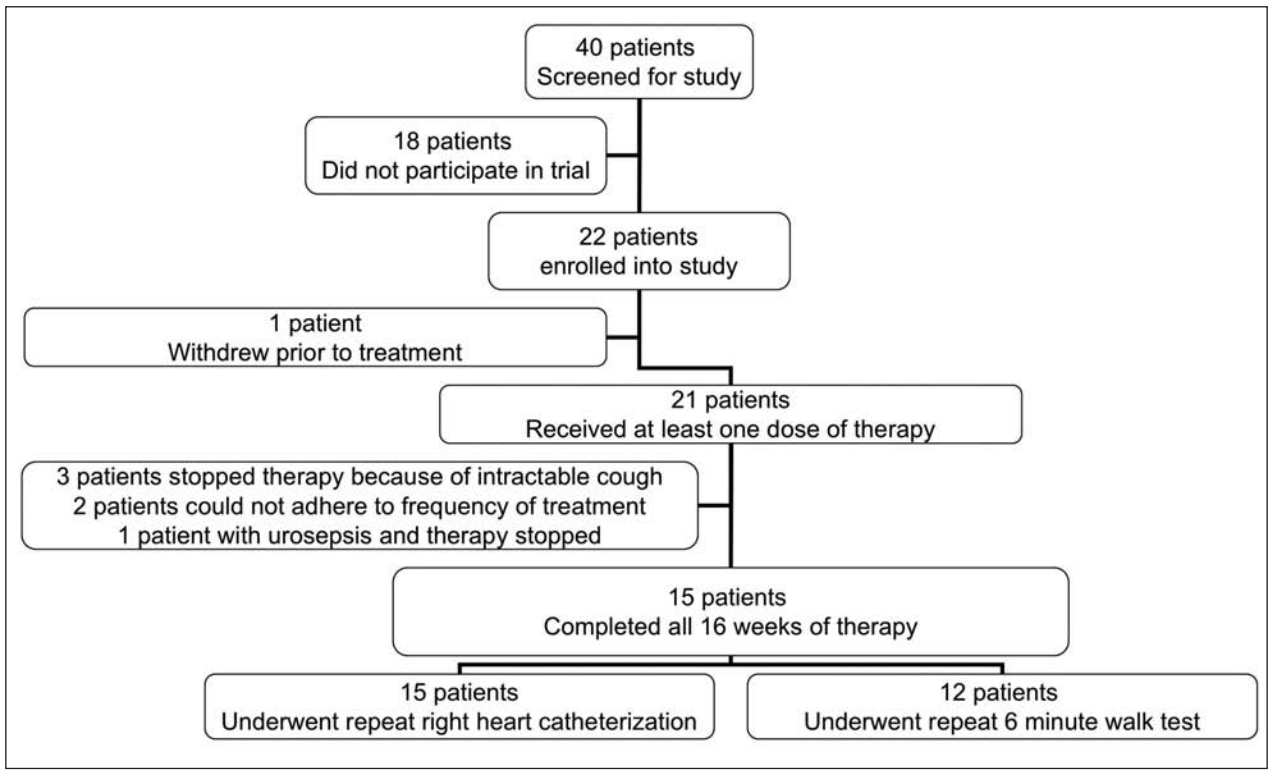

Fig. 1. Consort E-flow diagram of patients in study. Patients were seen every four weeks. All but three patients had follow-up six minute walk test done at least once on therapy.

Table 1. Demographics of patients enrolled in the study

Characteristic	All Patients	Those who completed treatment
Number	22	15
Male/Female	14/8	8/7
Black/White	21/1	15/0
Age (years)	52 (30-67)*	52 (41-67)
Duration of disease (years)	13 (1-62)	12 (6-62)
FVC (liters)	1.52 (1.14-3.48)	1.75 (1.14-3.48)
FVC % predicted	50% (41%-101%)	50% (41%-101%)
FEV-1 (liters)	1.17 (0.66-2.91)	1.08 (0.66-2.91)
FEV-1/FVC	73.2% (53.1%-90.8%)	74.4% (53.6%-90.8%)
Chest Roentgenographic stage		
Stage 0	1	1
Stage 1	1	1
Stage 2	2	1
Stage 3	3	1
Stage 4	15	11
Right atrial pressure (Torr)	7 (1-27)	7 (1-27)
PA systolic (Torr)	59 (30-85)	60 (30-85)
PA mean (Torr)	33 (20-62)	36 (20-62)
PAO (mmHg)	10 (4-15)	10 (4-15)
CO (liters/min)	5.9 (3.1-9.5)	5.4 (3.1-9.5)
PVR (Woods units)	5.1 (1.96-16.3)	6.1 (1.96-16.3)
6MWD (meters)	335 (23-488)	305 (23-306)

* Median (Range)

(median=11 years). All patients had received systemic sarcoidosis therapy, and all but one patient continued to receive systemic sarcoidosis therapy during the study. Systemic treatment included daily prednisone for 15 patients [10 mg (0-40 mg), median (range)], weekly methotrexate for 5 patients (10 mg in 4 cases, 20 mg in one case), daily azathioprine for 3 patients (25 mg for one patient, 50 mg for two patients), and one patient each on hydroxychloroquine (400 mg a day) and leflunomide (10 mg every other day). Five of the patients (23%) were classified as WHO functional class 2, 16 (72%) were classified class 3, and one patient withdrew from the study before evaluation.

Pulmonary function studies and chest roentgenograms demonstrated advanced disease in the majority of patients. Restrictive lung disease was documented in 20 of 22 (91%). Airflow obstruction was observed in the majority of patients, but no difference was observed in the level of obstruction between those patients who completed the study and those who dropped out early. One patient demonstrated only an obstructive defect. In only two patients was the chest roentgenogram staged as 0 or 1.

The initial cardiac hemodynamics of the 22 patients enrolled into the study are summarized in Table 1. The median PA mean pressure was 33 mm Hg and all but one patient had a PA mean of greater than 25 mmHg. In four patients, the right atrial (RA) pressure was greater than 10 mmHg. The one patient with an initial PA mean pressure measuring less than 25 mmHg experienced a significant increase in PA pressure to greater than 30 mmHg with exercise. The median pulmonary vascular resistance (PVR) was 4.55 (range 2.0-16.3 Woods units). The median 6MW distance was 335 meters, with a range from 23 to 488 meters. Eighteen of twenty-two patients (82%) demonstrated oxygen desaturation to less than 92% during the 6 MW. Only two patients did not report an increase in their Borg score after the 6 MW, and half of the patients reported Borg scores of greater than or equal to 5 during the 6 MW.

As shown in Figure 1, seven patients withdrew from the trial for various reasons including intractable cough in three patients and nonadherence to at least six treatments a day in two patients. One patient was withdrawn from the study because of prolonged hospitalization for urosepsis felt unrelated to drug and another patient withdrew for unspecified reasons prior to receiving the first dose of therapy. Of the remaining fifteen patients, all underwent repeat right heart catheterization after 16 weeks of

therapy. Only twelve patients repeated the 6 MW studies, and the remaining three patients did not repeat the 6 MW due to inability or unwillingness to perform the test.

The values for mean PA (Figure 2A) and PVR (Figure 2B) are shown for the initial and follow-up studies. Six patients experienced a 20% or greater decrease in PVR from baseline, and in five of these patients this was accompanied by a 5 mm Hg or greater reduction in PA mean. The mean change for the PA mean and PVR are shown in Table 2. At the end of the 16 week study, the WHO functional classification improved from 3 to 2 in four patients (27%) and worsened in one patient from 2 to 3.

As noted in Figure 3, improvement in 6MW distance was reported less frequently. The mean change in 6MW distance are shown in Table 2. During the course of the study, there was variability of the change in 6MW distance. After 16 weeks, three patients showed a 30 meter or greater increase in 6 MW distance. However, the cardiac hemodynamics improved in only one of these patients (decrease in PA mean by 6 Torr, decrease in PVR by 15.6%). In contrast, the other two patients who increased their 6 MW distances by 70 and 53 meters experienced increases in their PA mean pressures of 5 and 19 Torr, and increases in PVR of 98% and 57%.

Quality of life, including health related quality of life, were measured by several instruments: SF-36, SGRQ, SHQ, and FAS. As shown in Table 2, significant impairment of quality of life was observed at baseline for many patients. A FAS score of 22 or greater is considered clinically significant fatigue (17), and 17 patients had baseline FAS scores of 22 or greater. Likewise, a SGRQ score of 40 or greater is associated with significant impairment in respiratory health (15), and 15 patients had baseline total SGRQ scores of greater than 40.

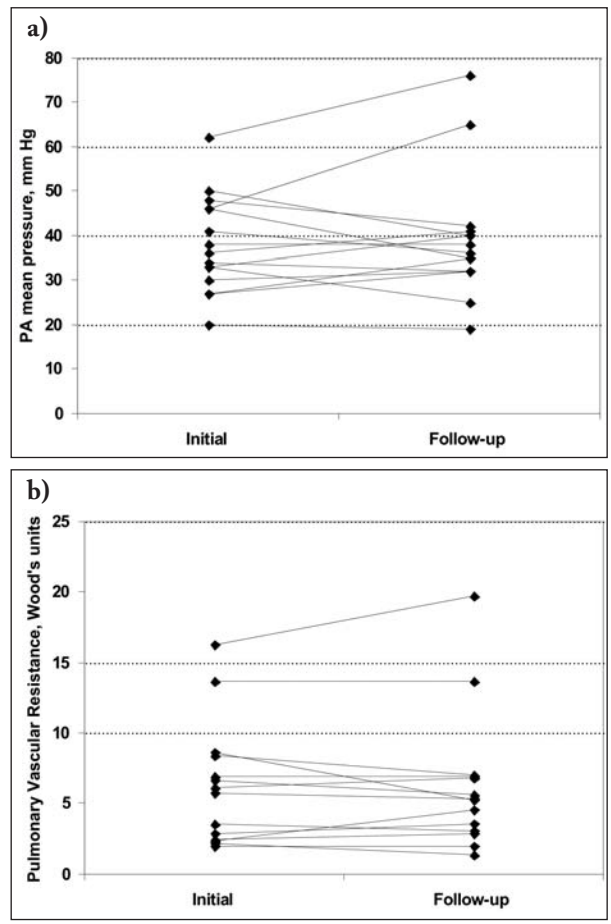

Fig. 2. The Initial and Follow-up hemodynamics on 15 patients treated with 16 weeks of inhaled iloprost. Figure 2A is pulmonary artery mean while Figure 2B is the pulmonary vascular resistance.

Based on baseline PA mean pressures of below or above 40 mm Hg, we divided our patients into two groups: mild to moderate and severe pulmonary arterial hypertension. As noted in Table 3, the eight patients with severe pulmonary artery hypertension walked significantly shorter 6MW distances. However, there was no significant difference between the

Table 2. Change in Pulmonary Hemodynamics with Iloprost Therapy

Measurement	Number of subjects	Mean ± Standard Deviation
PA mean change	15	+1.13 ± 0.864 mm Hg
PA mean percent change	15	3.3 ± 20.49%
PVR change	14 *	-0.47 ± 2.800 Wood Units
PVR percent change	14 *	-2.0 ± 40.79%
6MW distance change	12	0.6 ± 39.8 m
6MW distance percent change	12	2.5 ± 28.14%

* One patient did not have repeat cardiac output

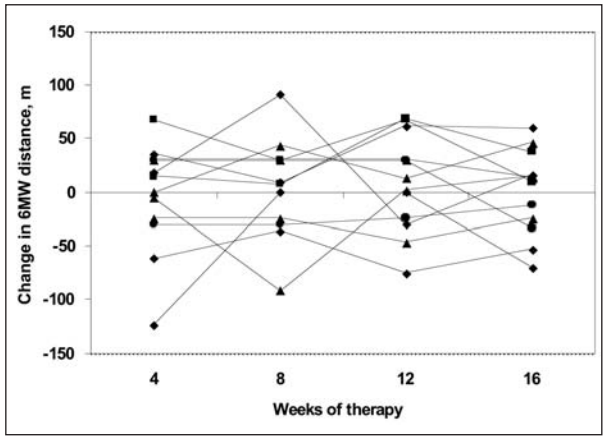

Fig. 3. Change in 6 minute walk distance (6MWD) in meters from the pretreatment value at four week intervals during therapy. All patients are represented for each visit they were seen.

two pulmonary artery pressure groups in the quality of life using the various instruments.

After 16 weeks of therapy, patients repeated all the quality of life instruments. Table 4 summarizes the results from the various instruments before and after treatment. Not all patients completed all questionnaires correctly. As noted in Figure 4, a significant decrease (p=0.0273) was reported in the SGRQ activity score. Seven patients experienced a 4 point or greater improvement in SGRQ activity score and no patient reported a worsening score of greater than 1 point. No other significant changes were reported by any other quality of life instrument. Additionally, no correlation existed between improvement in SGRQ score and with change in cardiac hemodynamics or 6 MW distances (data not shown).

As part of a post hoc analysis, we combined two of the predefined endpoints of the study: a change in the 6MWD and change in the pulmonary hemodynamics. For this analysis, we defined a response to treatment as either an increase in 6MW distance of 30 meters or greater or a decrease in the PVR by 20% or more. Eight of the fifteen (53%) patients who completed this trial experienced one or both of these response endpoints. These eight patients were considered "responders" and they were compared to the seven patients who did not respond, "non-responders". There was no difference between "responders" and "non-responders", in the clinical features of race, gender, age, duration of disease, or spirometric values. In addition, there was no difference in the quality of life measurements by any of the instruments.

At each visit, patients completed toxicity questionnaires. Cough was a frequent complaint and three patients withdrew from study because of intractable cough. Of the 15 patients who completed all 16 weeks, 14 complained of cough at week 16. The self-reported cough severity varied from level 1 for five patients, level 2 for four patients, and level 3 for five patients. Likewise the cough frequency ranged from level 1 in three patients, level 2 in two patients, level 3 in six patients, and level 4 in two pa-

Table 3. Perceived Quality of Life at Time of Enrollment in Study

	Initial	PAm<40 Torr	Pam≥40 Torr
Number	22	14	8
6MW distance, meters	335 (23-488) *	355 (23-488)	258 (53-366)¶
SF-36 total	31 (4-16)	31 (6-85)	59 (4-70)
SF-36 Physical Health	24 (5-56)	24 (5-80)	38 (5-61)
SF-36 Emotional Health	43 (3-86)	37 (4-83)	66 (3-86)
FAS	28 (19-50)	27 (16-50)	28 (25-38)
SGRQ Total	67 (46-73)	68 (30-80)	54 (32-76)
SGRQ Activity	86 (67-92)	85 (42-100)	83 (66-100)
SGRQ Symptoms	63 (35-81)	71 (32-90)	37 (28-75)
SGRQ Impact	52 (33-64)	57 (19-83)	41 (12-67)
SHQ Total	3.67 (2.95-4.46)	3.37 (2.12-5.38)	3.96 (2.46-5.63)
SHQ Daily	3.31 (2.96-4.45)	3.12 (1.77-5.85)	4.38 (1.46-5.77)
SHQ Emotional	4.20 (3.54-5.55)	4.10 (3.00-5.80)	4.50 (3.10-5.80)
SHQ Physical	3.00 (2.47-4.06)	3.00 (1.50-5.17)	367 (2.50-5.33)

* Median (Range)
¶ Differs from PAm<40 Torr p=0.0203
PAm=pulmonary artery mean pressure; 6MW=six minute walk; SF-36=short form 36; FAS=fatigue assessment score; SGRQ=Saint George respiratory questionnaire; SHQ=sarcoidosis health questionnaire

Table 4. Comparison of Quality of Life Results before and after therapy

	Number	Pre	Post
FAS	15	28 (19-50) *	31 (12-47)
SF 36 TOTAL	14	31 (4-61)	39 (12-64)
SF 36 PHYSICAL	14	23 (5-56)	34 (5-59)
SF 36 MENTAL	14	38 (3-69)	42 (10-75)
SGRQ Total	13	68 (35-79)	64 (38-95)
SGRQ Activity	13	86 (64-100)	74 (59-100) ¶
SGRQ Symptoms	13	66 (28-90)	55 (23-95)
SGRQ Impact	13	57 (18-67)	55 (24-92)
SHQ Total	14	3.55 (2.12-4.68)	3.83 (2.19-4.66)
SHQ Daily	14	3.23 (1.46-4.77)	3.69 (1.85-4.23)
SHQ Emotional	14	4.00 (3.00-5.80)	4.40 (2.90-5.30)
SHQ Physical	14	3.00 (1.50-4.50)	3.42 (1.83-4.83)

* Median (Range)
¶ Differs from pretreatment, Wilcoxon paired samples, p=0.0273

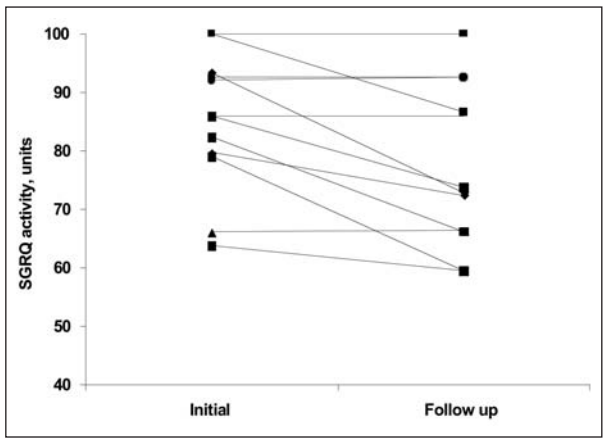

Fig. 4. The SGRQ activity score before and after therapy. Overall, there was a significant decrease in the score (p=0.0273)

tients. However, cough is a frequent problem for these patients as eight patients complained of cough at baseline prior to receiving study drug. This cough was characterized as level 3 in four cases and less severe in the other four cases. There was no change in the severity or frequency of cough in these eight patients. Although nausea was reported in six of fifteen patients at week 16, no patient discontinued the study because of this symptom. Severity of nausea was considered level 1 in four patients, level 2 in one patient, and level 3 in 1 patient. Frequency of nausea was level 1 in three patients, level 2 in two patients, and level 3 in one patient. In the three patients with baseline nausea prior to receiving therapy, no change occurred in the level of nausea with treatment. Of the patients who completed 16 weeks of therapy, six (20%) patients developed a new cough and three (10%) patients developed nausea while on inhaled iloprost. In addition, three patients withdrew from the study because of intractable cough. Overall 9 of 21(42%) patients who received any drug had significant cough. Other miscellaneous symptoms included mouth/lip sores in three patients, chest tightness in three patients, headache in two patients, and muscle spasms in one patient. None of these symptoms was sufficient to cause drug discontinuation. No change occurred in the FEV-1/FVC ratio throughout the study. At week 16, the post inhalation of iloprost FEV-1/FVC ratio was 79% (51.0%-89.7%, median (range)), which was not significantly different from the pretreatment values (Table 1, P=0.8394). In two patients the need changed for supplemental oxygen with one patient increasing from 2 liters per minute to 3 liters per minute and another patient who had not required supplemental oxygen requiring 2 liters per minute. No patient experienced syncope.

Discussion

Sarcoidosis associated pulmonary hypertension (SAPH) is a significant cause of persistent dyspnea in pulmonary sarcoidosis patients (1-3, 5, 21). To date, reports suggest that intravenous prostacyclines may benefit some patients (1, 7, 22). However, the intravenous route and side effect profile make these drugs difficult to use. One advanced disease patient reportedly failed to respond to inhaled iloprost (5). The current study prospectively studied 22 patients

with SAPH who received inhaled iloprost. Only fifteen patients could complete the 16 weeks of the study. Six patients (40%) had a >20% improvement in the pulmonary hemodyanamics, two had > 30 meter improvement in their 6MWD, and one patient had both. After 16 weeks of therapy, four patients demonstrated an improvement in their WHO functional classification while one worsened

The best assessment of response to vasodilator therapy remains unclear. While survival is perhaps the most important end point, the current study was neither of sufficient duration nor power to examine survival. Hemodynamics, 6 MW distance, and quality of life instruments have been proposed as surrogates in assessing response to treatment (11, 23). However, there remains no agreement on a single parameter to assess response to therapy (11).

In the current study, repeat hemodynamic studies performed after 16 weeks of therapy demonstrated a 5 mmHg or greater decrease in PA mean pressures in five (33%) of the patients who underwent repeat studies. A 20% or greater improvement in pulmonary vascular resistance was also measured in these five patients plus an additional patient. This prolonged benefit of inhaled iloprost after 16 weeks of therapy has been reported by others, with an average improvement in PA mean of 5-10 mmHg (20, 24, 25).

Five patients experienced an improvement in 6MW distance after 16 weeks of iloprost; however, only three patients demonstrated a 30 meter or greater improvement in 6MW distance. In studies of patients with idiopathic pulmonary arterial hypertension, the mean improvement in 6MW distance from baseline for iloprost treated patients varies from less than 30 meters (24, 25) to more than 70 meters (20). Sarcoidosis patients with pulmonary arterial hypertension walk shorter 6MW distances (12, 21). This may be the consequences of additional factors upon the 6MW distance, including pulmonary function and extrapulmonary issues, such as muscle strength and fatigue (12, 26). In reporting on the benefit of sildenafil alone, Milman et al also noted in their sarcoidosis patients that improvement in pulmonary hemodynamics was not associated with changes in the 6MW distance (9). Barnett et al reported on a group of sarcoidosis patients in whom vasodilator therapy was maximized for each patient (10). In that study, 11 of 22 patients had a >10% improvement in 6MWD. However, five patients had a greater than 10% reduction in 6MWD. Barnett et al reported follow-up hemodynamics in 12 of these patients. In these patients there was a significant improvement in pulmonary hemodynamics, with the average improvement 9 mm Hg and a forty percent reduction in pulmonary vascular response.

Preston et al examined the acute effect of intravenous epoprostenol on the pulmonary hemodynamics of patients with sarcoidosis (22). They found the drug led to a >20% improvement in PVR in four of six patients studied. Fisher et al noted an acute vasodilator response with reduction of PVR >25% in six of seven patients treated [7]. For six patients placed on long term intravenous epoprostenol therapy, five responded. In the current study, an inhaled prostacyclin was associated with a >20% reduction of PVR in 40% of cases.

A combined endpoint encompassing improvement in hemodynamics and/or improvement in 6MW distance has been proposed to better assess the response to therapy for pulmonary arterial hypertension (11). In our study, either one or both of these endpoints was achieved in eight of 15 patients. Four patients improved their WHO functional classification and one experienced worsening. This WHO functional classification change is similar to that reported in children treated with inhaled iloprost (27). Other studies report only a third of patients improving the WHO functional class during 16 weeks of therapy (25).

Prior studies suggest that patients with pulmonary arterial hypertension experience impaired quality of life (28). This assessment has included general quality of life as measured by the SF-36 (29-31) as well as heart failure specific questionnaires (30). In patients with pulmonary arterial hypertension the SGRQ score is also impaired (28, 29). Pulmonary arterial hypertension creates a greater impact on activity than other components of the SGRQ (29). In our study, the SGRQ activity score was significantly higher than that reported for normal healthy individuals, where the mean score is 7 (32). The higher SGRQ score indicates more severe impairment; and as noted in Table 2, the activity score was the highest baseline value of all three components of the SGRQ. We are aware of no prior longitudinal systematic reports evaluating the effect of pulmonary arterial hypertension on sarcoidosis

quality of life (30, 30, 33). Rather than using questionnaires specific for pulmonary arterial hypertension in this study, we chose instruments assessing quality of life focused on sarcoidosis specific questionnaires and the SGRQ, a respiratory oriented health related quality of life measure. This decision was based on our prior use of these instruments in studying various aspects of sarcoidosis, including 6 MW distance and fatigue studies (12, 34).

In seven patients, we demonstrated an improvement in the SGRQ activity score of 4 or more points with iloprost treatment of SAPH. This improvement probably represents a significant change as a four point or greater change is considered clinically significant in patients with chronic obstructive lung disease (15, 35) In unselected sarcoidosis patients, we previously noted that the SGRQ activity score was the only independent quality of life predictor of 6MW distance (12).

Few other studies have previously examined the change in quality of life with pulmonary artery hypertension therapy. One study reported an improvement with iloprost in the European quality of life instrument, but not in other measures of quality of life (36). However, the SGRQ was not evaluated in that study. An improvement in quality of life was reported in the Short Form 36 (SF-36) for patients in whom sildenafil was added to baseline epoprostenal therapy (33). However, no change for the entire treated population in the SF-36 was reported for sitaxsentan in one study (31), but a positive effect was noted in the subset with underlying collagen vascular disease (37). Exercise training has been shown to improve the SF-36 results (38). Several studies have failed to show improvement in other quality of life measurements during therapy for pulmonary arterial hypertension (28). Milman et al also noted in their sarcoidosis patients that improvement in pulmonary hemodynamics was not associated with changes in the 6MW distance.

Some patients in this study developed SAPH with little evidence for parenchymal lung disease. Two patients had no radiographic evidence of parenchymal lung disease, including one patient with a normal chest roentgenogram. Although the forced vital capacity was reduced in most patients, some patients had normal vital capacities. Other investigators have reported normal vital capacities in patients with SAPH (2, 39). In a study of patients with advanced pulmonary fibrosis due to causes other than sarcoidosis, inhaled iloprost was therapeutic (40). In the current study, no clinical features, including vital capacity, were identified that could predict response to iloprost therapy.

Barnett et al have reported that sarcoidosis patients with less extensive lung disease were more likely to respond to pulmonary vasodilators. In their retrospective analysis, they examined the change in 6MW distance for those with an FVC above and below the median for their group (51%). They found a significantly higher response for those with a FVC above the median (10). In our study, seven of fifteen patients who completed therapy had a FVC of greater than 51%. There was no significant difference in the 6MW distance or hemodynamics between those with higher versus lower FVC values. The Barnett et al study only 4 of 22 patients were treated with inhaled iloprost. Also, Barnett et al treated patients for a median of 14.7 months prior to the follow up 6MW test, with a range from 13 days to 52 months (10). Our study was a prospective study and all patients were evaluated after 4 months of therapy.

Cough was the most common complaint reported during this study. Nine patients developed new cough, including three patients who withdrew from the study because of cough. This was not surprising as cough has been reported a common side effect of inhaled iloprost when used for idiopathic pulmonary hypertension (24, 25, 36). In addition, cough is a common complaint of pulmonary sarcoidosis patients (41). Sarcoidosis can lead to airway obstruction (42) and endobronchial disease can be associated with cough (43). Inhaled prostacyclin can cause cough in normal subjects and asthmatics. However, it did not cause airway constriction (44). No changes were reported in the FEV-1 or episodes of bronchospasm associated with therapy during this trial. In addition, sore mouth and headache were noted by some patients. These complaints were seen more frequently for iloprost treated patients than placebo treated controls in randomized, double-blind studies (25, 36). Worsening ventilation perfusion mismatch has been reported with systemic prostacylin therapy in patients with interstitial lung disease (45). We did not specifically measure ventilation perfusion mismatch. In two patients, there was a need for increased supplemental oxygen after initiating iloprost therapy.

This prospective study found some patients with SAPH responded to inhaled iloprost as monotherapy. The drug was safe in sarcoidosis patients, even those with extensive lung disease. This drug may be more effective when used in combination with other agents (10).

Conflict of interest

Funded by Actelion. This is the only conflict of interest for all the authors involved in this study.

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