

ROFLUMILAST (DALIRESP®) TO REDUCE ACUTE PULMONARY EVENTS IN FIBROTIC SARCOIDOSIS: A MULTI-CENTER, DOUBLE BLIND, PLACEBO CONTROLLED, RANDOMIZED CLINICAL TRIAL

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ABSTRACT. Background: Fibrotic sarcoidosis patients often have acute events of increased cough and sputum production. We evaluated the impact of roflumilast in fibrotic sarcoidosis patients with repeated episodes of increased cough and sputum. **Methods:** Sarcoidosis patients with pulmonary fibrosis and at least two acute episodes in the previous year were randomized to receive either roflumilast (ROF) or placebo (PLA) in a double blind, placebo controlled multi-center trial. Subjects were assessed initially and every three months for 12 months. At each visit, spirometry and health related quality of life questionnaires were completed. For each subject, the best forced expiratory volume at 1 second (FEV-1) was noted. **Results:** Of the 38 subjects who enrolled in the study, 28 subjects (14 in each group) received at least three months of treatment and 10 in each arm completing all 12 months of study. During the treatment, patients treated with ROF were less likely to have visits in which the FEV-1 was less than 90% of the best FEV-1 (Odds ratio=0.34 (0.16 to 0.76 95% confidence interval, p=0.0073). At the end of treatment with ROF, patients had a significant improvement in their KSQ LUNG (Initial visit: 45.3 ± 6.89 (Mean ± S.D.); Last visit: 52.6 ± 7.91, p<0.05) with no change for PLA treated patients. **Conclusion:** Patients treated with at least three months of roflumilast had fewer follow-up visits with an FEV-1 of less than 90% of best value. At the end of treatment, ROF treated patients had a better quality of life as assessed by KSQ LUNG. **Clinical Trial Registration:** NCT01830959

KEY WORDS: fibrotic sarcoidosis, roflumilast, quality of life, spirometry

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ABBREVIATIONS

ROF - roflumilast

PLA - placebo

KSQ - Kings sarcoidosis questionnaire

KSQ LUNG - Kings sarcoidosis questionnaire lung

KSQ GH - Kings sarcoidosis questionnaire general health

LCQ - Leicester cough questionnaire

FEV-1 - forced expiratory volume in on2 second

FVC - forced vital capacity

OR - odds ratio

CI - confidence interval

COPD - chronic obstructive pulmonary disease

TDI - transitional dyspnea index

FAS - atigue assessment score

CONSORT - Consolidated Standards of Reporting Trials

INTRODUCTION

Pulmonary sarcoidosis has a wide range of outcomes from spontaneous resolution to progressive fibrotic disease (1). Between five and twenty percent of pulmonary sarcoidosis patients have pulmonary fibrosis on chest imaging (2-4). The rate of hospitalization and death from sarcoidosis has been rising over the past forty years (5;6). Patients with pulmonary fibrosis are at risk for dying from their disease (7-9). In addition, these patients with pulmonary fibrosis are more likely to have complications from their disease, often leading to hospitalization and significant morbidity (8).

A major cause of morbidity in fibrotic pulmonary sarcoidosis is acute pulmonary events of cough and sputum production (10). Patients often report wheezing and increased airway reactivity during these episodes. These events usually respond to 1-2 week treatment courses of antibiotics and/or increases in corticosteroid dosing (11). These events are similar to acute exacerbations encountered in chronic bronchitis (12). This is different than acute exacerbations that are seen with IPF (13). The outcome of acute exacerbations in obstructive lung disease are better than that seen in fibrotic lung disease (14). Although these acute events are self-limited for most sarcoidosis patients, they can be associated with significant morbidity. In one study, over seventy percent of fibrotic sarcoidosis patients reported two or more acute pulmonary events in the previous year (11). In that study, the frequency of acute events correlated with the presence of bronchiectasis but not with the severity of underlying lung disease.

To date, there are few criteria for acute events in pulmonary sarcoidosis. In a retrospective study, McKinzie et al identified 36 patients with acute pulmonary exacerbations at their institution. An acute exacerbation was defined as new or worsening pulmonary symptoms of cough, wheeze, chest pain, fever, or night sweats and documented decline of $\geq 10\%$ of either the forced vital capacity (FVC) or forced expiratory volume in one second (FEV-1) (15). In a study of 129 pulmonary fibrotic sarcoidosis patients, Baughman and Lower defined an acute worsening as an episode for which the patient was treated with a course of antibiotics and/or increased glucocorticoids for less than 28 days. That study did not evaluate lung function testing or imaging at the time of the event.

Panselinas and Judson (10) defined acute pulmonary exacerbations from sarcoidosis as decline of $\geq 10\%$ of either the forced vital capacity (FVC) or forced expiratory volume in one second (FEV-1) for more than one month. The one-month duration was to exclude patients with other events, such as asthma. We are aware of no prospective study evaluating lung function serially in fibrotic sarcoidosis patients to identify acute events.

Roflumilast, a phosphodiesterase-4 (PDE-4) inhibitor, has been shown to reduce the number of acute events in COPD patients (16;17). It has been shown to suppress oxidative stress and inflammation associated with acute infections (18). Additionally, reports suggest that the drug has immunosuppressive properties (19;20). Other PDE-4 inhibitors have been reported effective in treating sarcoidosis, including pentoxifylline for pulmonary sarcoidosis (21;22) and apremilast for cutaneous sarcoidosis (23). In a recent European Respiratory Society (ERS) evidence based guideline on treating sarcoidosis, use of these drugs for pulmonary sarcoidosis was not included because of insufficient data to date (24). Because of the potential benefit of roflumilast for exacerbations of both sarcoidosis as well as COPD exacerbations, we studied the effectiveness of roflumilast in reducing the number of acute events in chronic fibrotic sarcoidosis patients with a past history of repeated episodes of increased cough and sputum.

METHODS

This was a multi-center, double-blind placebo-controlled trial. Inclusion criteria included a diagnosis of sarcoidosis using standard criteria (25), an FEV1/FVC ratio of less than 80%, fibrosis on chest x-ray and/or high resolution computer tomography, have had at least two exacerbations of their sarcoidosis in the prior year. An exacerbation was defined as an acute event requiring increase of prednisone with or without use of antibiotics, on a stable dose of corticosteroids and other agents for their sarcoidosis at least 4 weeks prior to first visit. For patients on prednisone alone, the dose had to be the equivalent of 5 mg prednisone a day. For those on other immunosuppressants, they could be on any dose of prednisone. Patients had to be willing to take prednisone at increased dosage for exacerbation of their symptoms. Patients were between ages of 18 and 70

years of age.

Patients were excluded from the study if they had a known hypersensitivity to theophylline or pentoxifylline and did not receive theophylline or pentoxifylline during the time of the study. They were allowed to take drugs for sarcoidosis including prednisone, methotrexate, azathioprine, leflunomide, hydroxychloroquine, thalidomide, infliximab, adalimumab, and rituximab. Patients were excluded if their serum creatinine of greater than 3 mg/dL or they had moderate or severe liver disease as defined Child Pugh class 3 or 4, had unstable cardiac disease, or a non cutaneous malignancy treated in the past two years.

All subjects provided written informed consent of a protocol approved by the local Institutional Review Board. Data was captured using a research electronic data capture program (REDCap) (26). The trial was registered on ClinTrials.org as NCT01830959

After obtaining consent, subjects underwent an initial evaluation including a focused physical examination and spirometry. Subjects completed several patient reported outcomes measures (PROs) including the Kings Sarcoidosis Questionnaire (KSQ) (27) including KSQ LUNG and KSQ general health (KSQ GH) domains, Leicester Cough Questionnaire total score (cough related health status), (LCQ) (28), fatigue assessment scale (FAS) (29) and Transitional Dyspnea Index (TDI) (30).

Using a random sequence generator with block randomization for each of the three sites, subjects were subsequently randomized at a 1:1 ratio to receive either roflumilast (ROF) 500 mcg daily or placebo (PLA). Subjects were evaluated every three months for one year.

At each visit, the subjects underwent spirometry, completed PROs, and their medications were reviewed. Subjects with an acute worsening of pulmonary symptoms were identified and prescribed antibiotics and/or a short regimen of increased glucocorticoids if they had not already initiated therapy within the seven days prior to the visit.

Definition of an acute event: Acute events were defined in two ways. One method for defining an acute event was an episode in which an increase in corticosteroids and/or antibiotics were prescribed. This definition had been utilized in a prior study (11). The other method for defining an acute event was a clinic visit at which the FEV-1 was less than

90% of the patient's best value of all the subject's study clinic visits.

Statistics: The primary end point of the study was the reduction of the acute events over the time of the study. This was to be an intention to treat analysis. However, we could not further analyze those patients who attended only one study visit, since there was no paired data to calculate relative FEV-1 and PROs. Therefore, comparisons were made between the two treatment groups using the Student T test on subjects who were seen at least for three months of the study. Not all patients completed the 12 months of the study. For those who did not make the entire 12 months of the study, the last value was moved forward to calculate the changes between initial and end of treatment. Chi square analysis was used to calculate response rate. A p value of less than 0.05 was considered significant.

RESULTS

Thirty-eight subjects were enrolled in the study, 28 subjects received at least three months of therapy, and 20 subjects completed the full year of therapy (10 in each treatment group) (Figure 1). Figure 1 summarizes the outcome of the two assigned groups using the Consolidated Standards of Reporting Trials (CONSORT) form (31). There was no difference between the clinical features of those who completed the study and those who discontinued therapy early. Likewise, no significant difference was noted in the duration of treatment for the ROF versus PLA group (ROF=9.6 ± 3.37 months versus PLA=9.6 ± 2.92 months, p>0.05).

Table 1 summarizes the clinical features of subjects. For all patients who participated as well as those seen for at least three months, there were no significant differences between the ROF versus PLA subjects in terms of demographics, chest imaging, sarcoidosis organ involvement, or maintenance anti-sarcoidosis therapy. All patients had pulmonary fibrosis seen on HRCT, but we did not quantitate the amount of fibrosis found. Sixteen patients had bronchiectasis seen on HRCT (10 in ROF group and 6 in PLA group). Approximately half of the subjects were female and half were African American. All but one subject had received prednisone for their sarcoidosis, with 23 still on prednisone at time of study entry. Most subjects were receiving one or more

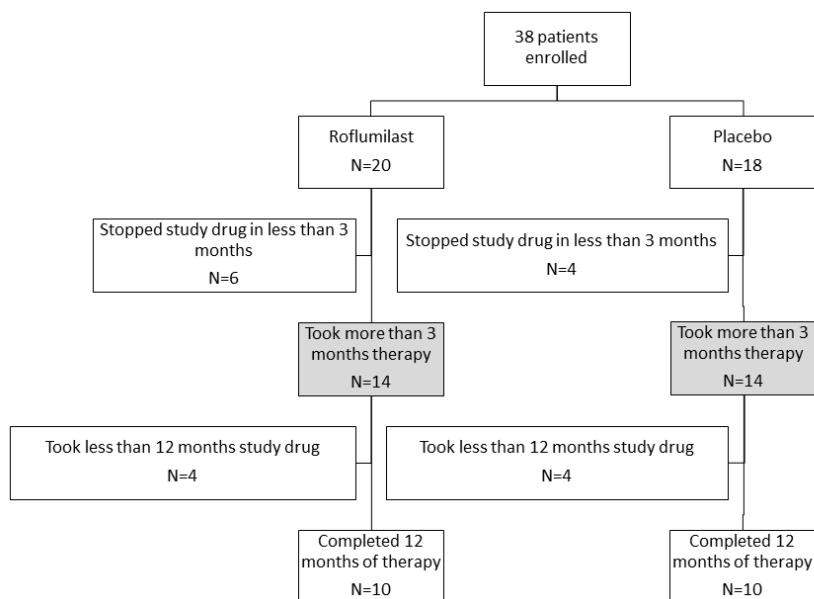


Figure 1. CONSORT (31) diagram of patients enrolled in study. Of the original 37 patients who enrolled in the study, 28 took at least three months of therapy (grey box) and 20 completed the full twelve months of treatment. Analysis was performed on the 28 patients who received at least three months of therapy.

corticosteroid sparing alternatives. In both groups, seven patients were prescribed an inhaled beta agonist and eight patients in each group were receiving inhaled corticosteroids. These therapies were kept constant throughout the study. The study included one current smoker (PLA) and 15 former smokers (7 PLA, 8 ROF). The clinical and PRO features of the smoker were not different from the other subjects, so that subject was included in further analysis.

Acute events: During the treatment phase of the study, acute events defined as a relative FEV-1% predicted < of 90% were recorded in 44 of 114 (38.6%) visits. These acute events were less likely to occur in the ROF treated subjects than the PLA group (Table 2, Chi square=7.191, p=0.0073). Subjects on ROF were less likely to have an acute event compared to the PLA treated group. The odds ratio for observing an acute event for roflumilast treated patients was 0.34 (95% CI: 0.157 to 0.756, Chi square=7.191, p=0.0073).

Defining an acute event as requiring treatment with a less than 30-day course of antibiotics or increased glucocorticoids was noted in 17 cases. There was no difference in the rate of treatment for the ROF patient (9 of 57 (15.8%) follow-up visits) versus PLA (8 of 57 (14.0%) follow-up visits).

Changes in spirometry and quality of life with treatment: Table 3 details the spirometry and quality

of life results at the initial and last visit for the 14 subjects in each group who were treated for at least three months. The values for the initial visit were compared to the last visit. There were no significant differences for the initial values between ROF and PLA groups. This included all 20 subjects who completed the full year of the study, as well as the eight who took at least three months of study drug. There were no significant changes from initial to last visit for any of the spirometry values for either the ROF or PLA group with therapy. Compared to the initial score, the KSQ LUNG increased by more than 7 points in the ROF group (Figure 2A, p<0.05) compared to minus 1.6 for the PLA patients (Figure 2B). For the LCQ, there was borderline significant improvement in the LCQ for the ROF patients (Figure 3A, p=0.07), but not for the PLA patients (Figure 3B). There were no significant changes for the KSQ GH, FAS, or TDI components for either treatment arm (supplement Table 1).

We evaluated the spirometry and PRO measurements for those subjects who were seen on a day of an acute event as defined relative FEV-1% predicted < 90% versus those with visits in which the relative FEV-1% predicted \geq 90%. We compared the spirometry and quality of life at these visits versus the subject's values on their initial visit prior to treatment (Table 4). For

Table 1. Clinical features of patients of all patients and those who took at least three months of therapy

	Roflumilast		Placebo	
	All patients	At least 3 months of therapy	All patients	At least 3 months of therapy
Number	19	14	14	14
Age, years (Median, range)	58 (38-67)	60 (38, 67)	59 (36, 76)	59 (36, 76)
Female	9	7	9	9
African American	9	7	6	6
Fibrosis on chest imaging	19	14	14	14
Other organ involvement †				
Skin	4	3	4	4
Eyes	2	1	2	2
Cardiac	0	0	2	2
Liver	1	0	2	2
Neurologic	1	1	0	0
Extra thoracic nodes	1	0	1	1
Therapy	Current/Past	Current/Past	Current/Past	Current/Past
Prednisone	15/4	11/3	16/3	12/2
Methotrexate	9/5	7/2	7/2	4/1
Azathioprine	2/2	1/0	1/2	1/2
Leflunomide	1/3	0/0	2/1	1/0
Mycophenolate	0/1	0/0	1/1	1/1
Hydroxychloroquine	0/4	0/3	1/1	1/0
Infliximab/Adalimumab	4/3	2/3	5/2	2/2

†Highly probable or at least probable using WASOG criteria (50)

Table 2. Effect of therapy on frequency of visits with an FEV-1 of less than 90% of best value

	Roflumilast	Placebo
% clinic visits without an event*	42 (74%)	28 (49%)
% clinic visits with an event	15 (26%)	29 (51%)

*Acute event is FEV-1 of 90% or less of maximal value. Chi Square=7.191, p=0.0073

those visits when the relative FEV-1% predicted was less than 90%, the absolute FEV-1 was lower for those with a relative FEV-1% predicted < 90% ($p < 0.005$) and the FEV-1 was almost 250 ml lower than the FEV-1 for those seen on days in which the relative FEV-1% predicted was > 90% ($p < 0.0001$). Likewise, there was an over 200 ml difference in FVC between the two groups ($p < 0.005$). There was a trend for the LCQ score to be higher (associated with better quality of life) for those subjects with a relative FEV-1% predicted of $\geq 90\%$ compared to those with an acute event ($p = 0.078$). However, there was no difference in

the KSQ LUNG, KSQ GH, FAS, or TDI questionnaires between subjects with and without an acute event (data not shown for KSQ GH, FAS and TDI).

Adverse events: Four subjects were hospitalized during the course of the study. Three of these subjects received roflumilast and one received placebo. Of the three subjects receiving roflumilast, one developed acute respiratory failure requiring intubation within a week of starting drug. He responded to antibiotics and increased prednisone, but did not receive further study medication. Another subject was hospitalized for respiratory failure within two weeks of starting study drug. This subject had confirmed influenza B, recovered uneventfully, and completed the year-long study. The last roflumilast treated subject was hospitalized at month 7 of the study for systemic hypertension. This was not felt to be related to study drug and subject remained in study for full year. One subject receiving placebo was hospitalized for acute respiratory failure at month 1 of treatment. While

Table 3. Spirometry and Quality of Life before and at end of treatment * of those who took at least three months of therapy

	Roflumilast initial		Roflumilast Follow-up		Placebo initial		Placebo Follow-up	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Spirometry								
FEV-1, L **	1.80	0.689	1.83	0.727	1.54	0.665	1.65	0.6633
FEV-1 % predicted	61.357	17.4867	63.929	20.6154	59	22.2987	64.214	23.5607
FVC, L	2.668	1.0126	2.631	1.009	2.446	1.033	2.496	0.9457
FVC % predicted	70.429	20.564	70.714	22.3553	69.786	16.6834	73.571	17.0867
Quality of life								
KSQ LUNG	45.3	6.89	52.6 ¶	7.91	53.1	17.63	51.7	22.46
LCQ	14.0	1.86	15.6 †	2.15	14.0	4.21	15.4	4.74

FVC: forced vital capacity; FEV-1: forced expiratory volume one second; LCQ: Leicester cough questionnaire; KSQ: King's sarcoidosis questionnaire. *Last value moved forward. **Pre bronchodilators. ¶ Compared to Roflumilast initial p<0.05. † Compared to Roflumilast initial p=0.07

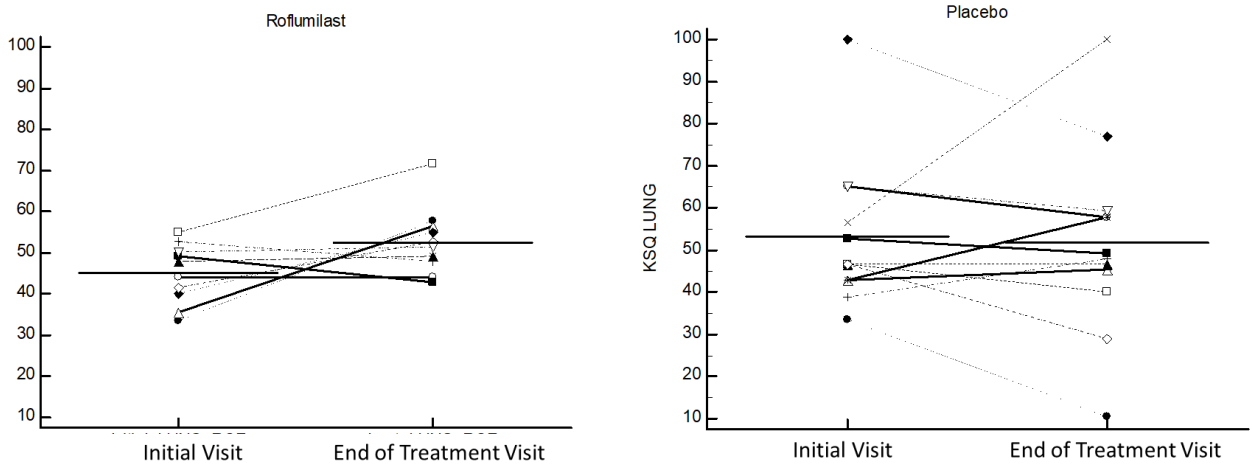


Figure 2. Values for initial and end of visit. At the end of treatment, the KSQ LUNG increased by more than 7 points in the ROF group (Figure 2A, p<0.05) which was not seen for the PLA patients (Figure 2B). Bar indicates mean value for each time period.

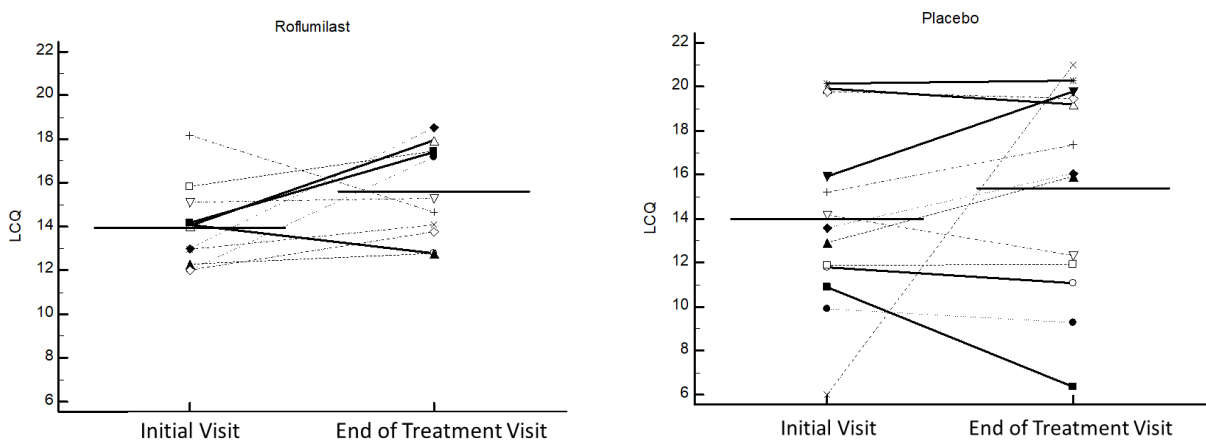


Figure 3. Values for initial and end of treatment visit. At the end of treatment, there was borderline significant improvement in the LCQ for the ROF patients (Figure 3A, p=0.07), but not for the PLA patients (Figure 3B). Bar indicates mean value for each timeperiod.

Table 4. Differences in FEV-1 and quality of life for visits with or without acute event *

Variable	FEV-1 \leq 90% of maximal value		FEV-1 $>$ 90% of maximal value		p
	Mean	SD	Mean	SD	
Absolute FEV-1, L	1.48	0.645	1.87	0.658	<0.005
Percent of initial FEV-1	78.1	13.59	96.7	3.76	<0.0001
Change in FEV-1 from initial visit , ml	-115	212.6	137	191.7	<0.0001
Change in FVC from initial visit, ml	-160	326.0	50	319.1	<0.005
Change LCQ from initial visit	-1.5	6.29	1.3	3.65	0.078
Change KSQ LUNG from initial visit	-1.5	6.29	-0.9	9.22	>0.10

FVC: forced vital capacity; FEV-1: forced expiratory volume one second; LCQ: Leicester cough questionnaire; KSQ: King's sarcoidosis questionnaire. *Acute event defined as an FEV-1<90% of maximal value.

the subject recovered from the event, the subject dropped out of the study. We also noted four subjects reduced their treatment dose by half due to diarrhea. All four subjects were on roflumilast and remained in the study on the lower dose.

DISCUSSION

In this study, sarcoidosis patients with pulmonary fibrosis and history of repeated acute events of cough and shortness of breath were randomized to receive either roflumilast or placebo for up to one year. We found treatment with roflumilast was associated with less documented visits with an FEV-1 of less than 90% of best value. Also, patients treated with roflumilast had improved quality of life as assessed by KSQ LUNG.

The clinical manifestations of acute pulmonary events in fibrotic sarcoidosis are increased cough, sputum production, and shortness of breath (11). These episodes are often treated with short courses of corticosteroids and broad-spectrum antibiotics (11;15). In contrast to acute exacerbations of idiopathic pulmonary fibrosis (13), these episodes usually resolve and are not felt to be associated with a worsening clinical course or increased mortality. The acute pulmonary events in sarcoidosis more closely resemble the acute exacerbations encountered in patients with chronic obstructive pulmonary disease (COPD) (32-34). Most all clinical drug trials in sarcoidosis have used endpoints comparing a physiologic, radiographic or quality of life measures before and after drug administration. However, many patients with chronic sarcoidosis are seriously impacted by exacerbations of disease that may not be reflected in "before versus after" endpoints (35).

In order to provide an objective measure of worsening pulmonary disease, we also examined the number of visits at which the FEV-1 was less than 90% of the patient's best value. We had previously used this definition for defining acute events since it provided objective evidence of lung function impairment (36). Compared to those subjects without a significant decline in FEV-1, visits with an FEV-1 of less than 90% of best value had lower FEV-1 and FVC of 250 and 200 ml respectively (Table 4). Subjects with reduced FEV-1 were more likely to have a worse LCQ result, although the difference was not significant.

This study found that roflumilast reduced the number of these acute events that occurred in fibrotic sarcoidosis patients. Roflumilast has been shown to reduce the number of acute exacerbations in COPD (16;17;37). In a meta-analysis, roflumilast reduced the exacerbations in COPD by an odds ratio of 0.82 (95% confidence interval (CI): 0.75 to 0.90) (37). In the current study, the rate of observed visits with an FEV-1 of less than 90% of best value for the placebo group was 51% versus 26% for the roflumilast group. The odds ratio for observing an acute event for roflumilast treated patients versus placebo was 0.34.

We also noted the number of episodes in which an increase in corticosteroids and/or antibiotics were prescribed. This definition had been utilized in a prior study to define acute events (11). There was no difference in the rate of these events between the two groups. This criterion is subjective and the events that are being treated can be due to many factors, including worsening of the underlying sarcoidosis (10).

In the current study, we found that treatment with roflumilast was associated with a significant improvement in quality of life as measured by KSQ

LUNG (Table 3). The KSQ LUNG for roflumilast treated patients rose by over 7 points while the KSQ lung fell in the placebo patients by 1.5 points (Table 3, Figure 2). The 7-point increase in the KSQ lung in the RFOF group is above the minimal clinical important difference (MCID) for KSQ LUNG which has been reported as 4 (27;38). There was a 1.6-point increase in the LCQ score for the ROF treated patients which was of borderline significance. The MCID of LCD has been reported as 1.3 (39). Improvement in quality of life has been reported in some, but not all, studies of roflumilast in COPD (40).

For more than twenty years, PDE-4 inhibitors have demonstrated efficacy in sarcoidosis. Pentoxifylline, a non-specific PDE-4 inhibitor, was first reported as effective in an open label single arm trial (22). A subsequent double blind placebo controlled trial of pulmonary sarcoidosis found that pentoxifylline was steroid sparing when compared to placebo (21). That study did not demonstrate significant improvement in pulmonary function for the treated patients. Apremilast, a new generation PDE-4 inhibitor, was beneficial in treating chronic cutaneous sarcoidosis (23). In vitro studies have demonstrated that pentoxifylline suppresses alveolar macrophage release of tumor necrosis factor (TNF) (41;42). Suppression of TNF release by alveolar macrophages has been demonstrated after successful treatment of pulmonary sarcoidosis with either prednisone or methotrexate (43). Monoclonal antibodies directed against TNF, such as infliximab, have been shown to improve lung function in chronic pulmonary (44;45) and cutaneous sarcoidosis (46). Although our study failed to detect improvement in lung function or extra-pulmonary sarcoidosis, it was not designed to examine the effect of one year of roflumilast therapy on sarcoidosis itself but rather on the risk of exacerbations.

Significant gastrointestinal distress leading to drug discontinuation was reported in over ten percent of the pentoxifylline treated patients (21;22). Roflumilast has also been associated with gastrointestinal distress in some patients. A meta-analysis of roflumilast trials for COPD calculated the odds ratio of 4.5 for roflumilast-related diarrhea and 3.8 for roflumilast-related nausea compared to placebo treated patients (37). In this study, we reduced the study drug dose to 250 mg for four subjects receiving

roflumilast and none of the placebo treated subjects because of gastrointestinal issues. No other unanticipated side effects were noted in the study.

Acute respiratory decompensation requiring hospitalization was observed in three subjects (two on roflumilast and one on placebo). These events occurred within the first month of study participation and at least one was participated by influenza B infection. These events seemed unrelated to study drug.

The study was limited by the fact that almost half of subjects failed to complete the full one year of the study. The drop-out rate was the same for both roflumilast and placebo treated subjects, suggesting that underlying conditions and patient preference were important factors in study retention. Because a significant proportion of roflumilast subjects developed gastrointestinal toxicity, study retention might have improved with a lower initial dose of 250 mcg followed by increased dosing after four weeks (47). The study may have been underpowered to detect a significant difference in LCQ, although there was a trend for improvement of cough with roflumilast. Our definition of acute events using an FEV-1 of less than 90% needs to be further validated as an endpoint. In addition, the FEV-1 was only measured at study visits and other events may have been missed. Although all patients had fibrosis on HRCT, we did not quantitate the amount (or distribution) of fibrosis. We were unable to determine whether HRCT findings would predict clinical outcome in this study. The overall number of patients was too small to determine whether the presence of bronchiectasis affected response to therapy. We also did not collect DLCO or TLC data. Our study was designed to evaluate the potential of roflumilast in reducing the number of acute events in sarcoidosis patients with pulmonary fibrosis. In a prior study, we noted that these acute events could occur in patients with or without airflow obstruction. Roflumilast has been shown to be effective in chronic airway obstructive disease, including those already receiving bronchodilators and inhaled corticosteroids. We felt that roflumilast was more likely to be effective in sarcoidosis patients with airway obstruction (16;48). Therefore, the study only included those with an FEV1-/FVC of less than 80% and we did not exclude those receiving inhaled treatment for their airway obstruction. Recently it has been observed that fibrotic sarcoidosis patients may have a mixed pattern of obstruction and restric-

tion, with a reduced FEV-1/FVC and low total lung capacity (TLC) (49). In that study, patients with a mixed pattern had a worse outcome than those with only obstruction. Since we did not measure TLC, we cannot analyze the effectiveness of roflumilast in the two different groups. Future studies should consider evaluating the two groups separately.

Because of the few studies to date, the recent ERS treatment guidelines was not able to make specific recommendations regarding the use of PDE-4 inhibitors for pulmonary sarcoidosis. They did comment on use for cutaneous sarcoidosis (24). These guidelines supported future trials to look at novel therapies for sarcoidosis and to evaluate treatments that may improve quality of life. This small study was able to demonstrate a reduction in acute events and an improvement in quality of life for those patients receiving roflumilast. We feel these studies should lead to a larger study confirming these findings.

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RPB had full access to all the data in the study and takes responsibility for the content of the manuscript, including the data and analysis. RPB, EEL, MAJ, and DAC contributed substantially to study design. RPB, MAJ, DAC, JP, JZ, and EEL contributed substantially to data acquisition. RPB, SB, EEL, MAJ, and DAL contributed substantially to data analysis, interpretation, and writing of the manuscript

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