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# Value of pulmonary function testing identifying progressive pulmonary disease in fibrotic sarcoidosis: results of a prospective feasibility study

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To the Editor,

Advancing pulmonary fibrosis is the most frequent cause of death from sarcoidosis (1,2). While some patients with fibrotic sarcoidosis remain stable or improve with anti-inflammatory therapy, antifibrotic treatments have not been evaluated definitively. However, it appears likely that they will provide benefit. Up to twenty percent of pulmonary sarcoidosis patients develop progressive fibrosis that may lead to a decline in lung function, respiratory failure, and death (2,3). To date, there is little information on how to identify fibrotic sarcoidosis patients who progress despite anti-inflammatory therapy. Retrospective studies have found increased risk of mortality for patients with >20% fibrosis on high resolution computer tomography (HRCT), reduced DLCO, or increased composite physiologic index (CPI) score (3,4). We evaluated the feasibility of using one or more of these features to predict clinical worsening over an 18-month prospective study.

This was a multi-center double-blind, placebo-controlled feasibility study of pirfenidone for patients with significant fibrotic pulmonary sarcoidosis. Patients were recruited from three US sites (the University of Cincinnati Medical Center, Temple University Hospital, and Albany Medical College). Enrollment criteria included a diagnosis of sarcoidosis based on ATS/ERS/WASOG criteria (5) more than >20% fibrosis on high resolution CT scan (6), age between 18 and 90 years, and not being listed for lung transplantation. Patients were required to be receiving stable glucocorticoid therapy for sarcoidosis for at least one month and no change in other immunosuppressive therapy in the two months prior to study entry. Patients were excluded if they were receiving therapy for moderate to severe precapillary pulmonary hypertension as defined as a mean pulmonary artery (mean PA) pressure of greater than 35 mm Hg (7). Patients with mild pulmonary hypertension (mean PA < 35 mm Hg) with or without therapy could participate if there had been no change in their treatment for pulmonary hypertension in the preceding three months. Patients were excluded who had a clinically significant co-existing disease which in the opinion of the investigator was likely to affect their 18-month survival. All patients provided written consent of an Institutional Review Board approved document. The study was registered on ClinicalTrials.gov (NCT03260556).

Patients underwent chest computed tomography scan (CT), spirometry, and DLCO within six months of study entry reviewed locally for screening. The %

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predicted for FEV-1, FVC, and DLCO were calculated using standard height, sex, age and race corrected formulas (8,9) and the CPI was then calculated (4,10). A six minute walk test (6MWT) was performed using a standard protocol (11) to determine 6-minute walk distance (6MWD). For the baseline 6MWT patients used the level of supplemental oxygen they had been using for exercise. This level of supplemental oxygen was used for all the follow-up 6MWTs.

Health related quality of life (Harmol) was assessed using the Short Form 36 (SF-36) and the disease specific King's Sarcoidosis Questionnaire (KSQ) (12). Additional HRQoL instruments that were measured included the Fatigue Assessment Score (FAS) (13) and the King's Brief Interstitial Lung Disease questionnaire (K-BILD), a quality of life instrument specific for interstitial lung disease (14). Dyspnea was assessed using the Medical Research Council (MRC) dyspnea scale (15). Patients were randomized to pirfenidone (PIRF) or placebo (PLA) at a two to one ratio using a central investigational pharmacy which block randomized each site for three patient blocks. The dosage of pirfenidone (or placebo) was increased from one 267 mg capsule (or placebo) three times a day to three capsules three times a day over a four-week period as tolerated. Patients were seen every 3 months with spirometry and 6MWD performed at each visit up to a total of 18 months of treatment.

Because of new European Union and Great Britain regulations leading to exclusion of participation of these sites and the temporary closure of study sites due to the COVID-19 pandemic, the study was terminated early. A clinical worsening event (CWE) was defined by one of the following: death, lung transplant, or > absolute 10% drop in % predicted FVC. Kaplan-Meier curves were calculated for the time to clinical worsening (TCW) defined as the time from study entry until the CWE or the end of treatment. Comparisons between groups were made using Log Rank test. Group comparisons were made using Mann-Whitney U test for continuous data, Fisher's exact test for group proportions, and log rank for Kaplan Meier curves. Ap value of <0.05 was considered significant. Statistics were calculated using MedCalc® Statistical Software version 20.015 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Sixteen patients were enrolled, and block randomized so that patients at each site received either PIRF or PLA in a 2:1 ratio. One PLA patient withdrew before receiving the first dose of study drug. One patient withdrew after 98 days because of transportation issues, the remaining 14 patients completed the 18 months of study. Overall, four patients had a CWE (1 death, 1 lung transplant, 2 with >10% absolute change in FVC % predicted). All four CWE patients had been treated with pirfenidone. The initial DLCO % predicted was significantly lower for those who had a CWE ($p<0.02$). For those who had a CWE, there was a significant worsening of KBILD lung ($p<0.05$). There were no significant differences between the groups in terms of any of the other pulmonary function or HRQoL measurements.

There was a significant difference in the probability of achieving a CWE for four DLCO cohorts: <30% predicted, 31-40% predicted, 41-60% predicted, and >60% predicted (Log Rank Chi square=8.1741, $p<0.05$). There was a significant difference in the proportion of patients with a DLCO <30% who had a CWE (4/6, 67%) compared to patient with a DLCO >30% (0/9 with a CWE, Fishers exact test, $p<0.02$). Table 1 summarizes the initial features of patients with a DLCO < 30% versus those with >30% predicted. The absolute and % predicted DLCO % predicted and the CPI score, which includes the DLCO % predicted, were significantly worse for those with a DLCO <30% predicted. The 6MWD was also a significant lower for those with a DLCO < 30% predicted ($p<0.05$). All other parameters in Table 1 were not statistically different between the two groups.

Of the four patients with a CPI score <40, none had a CWE versus two of six with a score between 41 to 60 had a CWE versus two of five of those with a CPI >60 having a CWE. There was no significant difference between the three cohorts of CPI.

Of the 11 PIRF patients, one withdrew after 98 days because of transportation issues. Of the remaining 10, four developed a CWE (1 death, 1 lung transplant, 2 with >10% absolute change in FVC % predicted) and the other six completed 18 months of therapy. Of the 5

**Table 1.** Baseline clinical parameters based on DLCO ≤ vs > 30% predicted

| | **DLCO ≤ 30% predicted** | **DLCO >30% predicted** |
|---|---|---|
| **Number** | 6 | 9 |
| | Median (range) | Median (range) |
| **FVC, l** | 1.20 (0.62-3.08) * | 2.17 (1.20-2.78) |
| **FVC % predicted** | 47 (27-68) | 58 (47-73) |
| **FEV-1, l** | 0.72 (0.45-1.59) | 0.94 (0.79-2.28) |
| **FEV-1 % predicted** | 29 (21-61) | 50 (25-70) |
| **FEV-1/FVC %** | 63 (37-81) | 68 (33-82) |
| **DLCO, mm Hg §** | 6.06 (3.78-21.00) | 11.52 (9.6-17.10) |
| **DLCO % predicted †** | 20.5 (19.0-29.0) | 56 (31-70) |
| **CPI †** | 65.4 (57.0-72.8) | 43.61 (23.4-62.4) |
| **6MWD, m §** | 190 (90-305) | 350 (183-454) |
| **KSQ GH** | 54 (49-100) | 62 (54-91) |
| **KSQ_Lung** | 54 (43-100) | 55 (40-65) |
| **KBILD_Lung** | 64 (44-100) | 64 (32-85) |
| **KBILD_Total** | 52 (38-78) | 53 (42-78) |
| **MRC** | 3 (0-4) | 2 (1-4) |
| **FAS** | 21 (11-27) | 22 (11-36) |
| **SF-36_Mental Health** | 51 (16-65) | 70 (50-94) |
| **SF-36_Physical Health** | 31 (9-49) | 51 (21-83) |
| **SF-36_Total** | 42 (14-61) | 61 (42-87) |
| **Female:Male** | 4:2 | 5:4 |
| **African American:Caucasian** | 5:1 | 5:4 |

*Median (range); § Significant difference between groups, p<0.05; † Significant difference between groups, p<0.005; FVC: forced vital capacity; FEV-1: forced expiratory volume in one second; DLCO: diffusion lung carbon monoxide; CPI: composite physiologic index; 6MWD: six minute walk distance; KSQ: King's sarcoidosis questionnaire; KBILD: King's Brief Interstitial Lung Disease questionnaire; FAS: fatigue assessment scale; SF-36: short form-36

PLA patients, one withdrew prior to any therapy. The remaining four all completed 18 months of therapy without a CWE. There was no significant difference in the Kaplan Meier curves for TCW between the two treatments (Log Rank Chi square=1.469, P>0.05). There were no serious adverse events recorded for either treatment groups.

To summarize these data, we found that one-quarter of pulmonary fibrotic sarcoidosis patients with more than 20% fibrosis on HRCT had a CWE during the 18 months of treatment. There was a significant difference in the initial DLCO % predicted for those who had a CWE and those who did not. The use of a reduced DLCO threshold for enriching future studies of fibrotic pulmonary sarcoidosis may reduce individual variability in outcome of patients with stage 4 disease.

Previous large retrospective studies found that markers for pulmonary hypertension and extensive pulmonary fibrosis were independent risk factors for mortality in pulmonary sarcoidosis (3;4;16). While treatments have been studied for sarcoidosis associated pulmonary hypertension, there have been limited studies in treating progressive fibrosis in sarcoidosis. A study of nintenanib for progressive pulmonary fibrosis included a limited number of sarcoidosis patients, with only three receiving active drug.

Our original sample size was to be 60 patients. However, only 16 were enrolled because of new European Union and Great Britain regulations leading to exclusion of participation of these sites and the temporary closure of study sites due to the COVID-19 pandemic. Because of slow patient recruitment, the study was underpowered to detect a difference between treatment arms. We therefore converted the study to a feasibility trial to assess the role of pulmonary function testing in identifying pulmonary fibrotic sarcoidosis patients who would reach a CWE over the 18 months of the study.

In summary of this prospective study of pulmonary sarcoidosis patients with at least 20% fibrosis on chest CT, we found a DLCO of <30% added value to the findings of HRCT alone in predicting the development of a CWE within 18 months. While no patient with a CPI score of <40 had a CWE, the CPI was not as discriminating as DLCO. This feasibility study suggests that future treatment studies of progressive pulmonary fibrosis should focus on those with significant fibrosis on HRCT. The DLCO provides additional value to the radiographic findings.

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