Outcomes for Patients With Sarcoidosis Awaiting Lung Transplantation*

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Study objectives: To describe the population of patients with sarcoidosis listed for orthotopic lung transplantation (OLT) in the United States, and to determine outcomes for these subjects relative to persons awaiting OLT for idiopathic pulmonary fibrosis (IPF).


Patients: All patients listed for OLT with an underlying diagnosis of either sarcoidosis or IPF.

Measurements and results: During the study period, 427 patients with sarcoidosis and 2,115 patients with IPF were registered on the list for OLT. Demographically, the patients with sarcoidosis were younger and more likely to be female African Americans than were patients with IPF. Pulmonary function was worse in patients with sarcoidosis. The mean FVC was 42.6% of predicted, as compared to 45.0% of predicted in patients with IPF (p = 0.0044). The FEV1 also differed between the populations (36.0% vs 46.0% of predicted for patients with sarcoidosis and IPF, respectively; p < 0.0001). Only 30.1% of patients with sarcoidosis and 32.4% of patients with IPF lacked functional limitations. For the subset of patients with hemodynamic data available, the mean pulmonary artery pressure was significantly higher in the sarcoidosis population (34.4 mm Hg vs 25.6 mm Hg, respectively; p < 0.0001). Neither the pulmonary capillary wedge pressure nor the cardiac index differed between the groups. Patients with sarcoidosis were less likely to receive a transplant. Approximately 30% of patients with sarcoidosis underwent OLT, compared to 37.3% of IPF patients (p = 0.0102). For those who did undergo transplantation, the median wait until OLT was 803 days for patients with sarcoidosis compared to 555 days for patients with IPF (p < 0.0001). Mortality rates were similar in both groups. In the sarcoidosis group, 28.1% of patients died, compared to 31.1% of patients with IPF (p = not significant).

Conclusions: Patients with sarcoidosis are at as high a risk for mortality as patients with IPF while awaiting transplantation. Nonetheless, patients with sarcoidosis are less likely to undergo OLT. Pulmonary hypertension is a major concern in patients with advanced sarcoidosis awaiting transplantation.

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Key words: idiopathic pulmonary fibrosis; lung transplantation; pulmonary hypertension; sarcoidosis

Abbreviations: CI = confidence interval; IPF = idiopathic pulmonary fibrosis; NS = not significant; OLT = orthotopic lung transplantation; UNOS = United Network for Organ Sharing

Sarcoidosis is a multisystem disease of unknown etiology that predominantly affects the lungs and intrathoracic lymph nodes. Noncrotizing granulomas are found in affected organs, and T-cell function plays a role in the development of sarcoidosis.1 In some patients, the disease comes to attention because of incidental findings on chest radiography, while in others it produces significant clinical symptoms.2 For patients requiring treatment, corticosteroids remain the mainstay of therapy.3,4 The majority of patients who receive corticosteroids do well, in that their symptoms and lung function either improve or stabilize.3 Despite treatment, however, some individuals with sarcoidosis progress and end-stage lung disease develops. Radiographically, such patients have parenchymal fibrosis and scarring.5 Clinically, these patients have significant dyspnea, exercise intolerance, and may need supplemental...
oxygen. Of patients who die from sarcoidosis, approximately 75% do so because of advanced lung disease.6

Treatment options for end-stage sarcoidosis are limited. By the time fibrosis develops, active inflammation that might be responsive to either corticosteroids or other immunomodulatory agents, such as methotrexate, may no longer be present.7 Aside from supportive care and pulmonary rehabilitation, orthotopic lung transplantation (OLT) may be the only other option for end-stage sarcoidosis.8 Organ transplantation is now an accepted approach to patients with chronic organ failure, and is increasingly offered to patients with a number of different chronic respiratory diseases, such as cystic fibrosis, COPD, and idiopathic pulmonary fibrosis (IPF). Patients with such illness constitute the majority of patients undergoing OLT. Therefore, little is known about patients listed for OLT for sarcoidosis. Several small series describing outcomes for patients needing OLT for sarcoidosis have been published, and these suggest that patients with sarcoidosis may do well with OLT, despite the possibility that the disease may recur in the transplanted lung. Nonetheless, no formal guidelines exist to aid clinicians in determining when to refer patients with sarcoidosis for an OLT. Additionally, although patients who receive a lung transplant for sarcoidosis appear to do as well as patients who receive transplants for other diseases, data describing outcomes for patients with sarcoidosis awaiting OLT are lacking. If patients with sarcoidosis listed for OLT fare as poorly as do patients with IPF, it may be necessary to determine if patients with sarcoidosis require a waiting-time credit. Presently, patients with IPF receive a 90-day credit when formally listed for transplantation.

Furthermore, end-stage IPF and sarcoidosis appear similar in several respects. CT scans in patients with either disease may demonstrate fibrosis, honeycombing, and traction bronchiectasis.5 Patients with both IPF and sarcoidosis may also have severe restriction on spirometry and hypoxemia. Given these likenesses, we hypothesized that patients with sarcoidosis listed for OLT would have survival rates similar to those for patients with IPF. To test this hypothesis and to better describe the characteristics of the population of patients with sarcoidosis awaiting OLT, we conducted a comparative retrospective study of patients with IPF and sarcoidosis who were on the waiting list for OLT in the United States between 1995 and 2000.

Materials and Methods

Subjects and End Points

The United Network for Organ Sharing (UNOS) maintains a registry of all patients listed for organ transplantation in the United States. We reviewed this registry and identified all persons registered with either sarcoidosis or IPF who were on the OLT list between January 1995 and December 2000, regardless of initial listing date. The diagnosis of either IPF or sarcoidosis was based on the reports of the referring transplant centers. Patients listed for any form of possible OLT (single lung, bilateral lung, or heart-lung transplant) were included in the study cohort. The primary end point for this study was time until transplantation, defined as the period between listing and placement of the organ. Death rates while awaiting OLT comprised a secondary end point.

Study Variables

Data regarding patient demographics (age, gender, and race) were recorded. In addition, information concerning functional status, pulmonary function, and vascular comorbidities was abstracted. Patients were categorized as either having no activity limitations, able to perform activities of daily living with assistance, or hospitalized for purposes of assessing functional status. For pulmonary function both the FEV1 and the FVC were examined. The UNOS does not record data regarding the diffusion capacity of the lung for carbon monoxide, and only began noting the FEV1/FVC ratio in 1999. Hence these variables were not included in the analysis. Other pulmonary variables included 6-min walk distance (either > 150 feet or < 150 feet), the PCO2, and the need for supplemental oxygen. For vascular disease, we determined if hypertension, angina, cerebrovascular disease, or peripheral vascular disease were present. When available information regarding pulmonary artery pressures, the pulmonary capillary wedge pressure, and cardiac index were also noted. Finally, we determined if IV antibiotics for a pulmonary infection were needed more than once in the 12 months prior to listing, and whether the patient was dependent on corticosteroids. Corticosteroid dependency was considered present if the patient needed therapy with > 5 mg of prednisone (or equivalent) daily. The use of corticosteroids was at the discretion of the listing institution. For each of the variables listed above, data were abstracted from information available at time of listing for OLT. Therefore, the analysis does not reflect either the development of new processes while awaiting OLT (eg, suffering a new cerebrovascular accident) or worsening (eg, decline in functional status) in other variables while on the transplant list.

Statistics

Continuous data are reported as mean ± SD. Categorical variables were compared with the χ² test. For continuous variables, we assumed all followed a nonparametric distribution. Therefore, a Wilcoxon rank-sum test was employed. All tests were two-tailed, and a p value of < 0.05 was assumed to represent statistical significance. The log-rank test was used to compare the probability of undergoing transplantation in the 2 years following listing. We computed Kaplan-Meier curves to compare survival rates between IPF and sarcoidosis patients. Ninety-five percent confidence intervals (CIs) are reported where appropriate. Analyses were done using software (SAS version 8.0; SAS Institute; Cary, NC).

Results

During the study period, 12,228 patients in the United States were listed with the UNOS for OLT. Of these, 427 patients (3.5%) were listed for sarcoi-
sarcoidosis, while 2,115 of these patients (17.3%) had IPF. As shown in Table 1, patients with sarcoidosis were significantly younger than the patients with IPF (45.4 ± 8.5 years vs 51.4 ± 9.6 years; p < 0.0001). Patients with sarcoidosis were also predominantly female African Americans (66.0% female, 70.3% African American), while the IPF cohort was comprised mainly of white male subjects (60.7% male, 79.5% white). These differences in demographics were highly statistically significant (for both analyses, p < 0.0001).

Also shown in Table 1 are comparisons for pulmonary function. Patients with sarcoidosis had worse spirometry findings. FVC was 42.6 ± 13.8% of predicted for patients with sarcoidosis vs 45.0 ± 14.2% of predicted for patients with IPF (p < 0.0035). Similarly, the FEV1 was 36.0 ± 14.4% of predicted in patients with sarcoidosis as compared to 46.0 ± 16.7% of predicted in patients with IPF (p < 0.0001). The mean PCO2 was slightly higher in patients with sarcoidosis (42.3 mm Hg), while it was 40.1 mm Hg for patients with IPF (p < 0.0001). However, patients with sarcoidosis required less supplemental oxygen (2.4 ± 1.9 L/min vs 2.8 ± 2.2 L/min, respectively; p = 0.0029). Despite these differences in pulmonary function, the proportion of patients with either sarcoidosis or IPF with 6-min walk distances of <150 feet were comparable (12.2% vs 13.0%, respectively; p = not significant [NS]). Additionally, although there was no difference in performance status between the sarcoidosis and IPF groups, few patients in either category lacked functional limitations (30.1% of sarcoidosis patients vs 32.4% of IPF patients; p = NS). Approximately one half of the patients in both cohorts were only able to perform activities of daily living with assistance (p = NS).

For vascular comorbidities, the overall prevalence of these processes was low. Nonetheless, hypertension and cerebrovascular disease were more common among patients with sarcoidosis. Peripheral vascular disease was uncommon in all subjects (<1.2% for either disease). Patients with IPF, however, were 2.93 times (95% CI, 1.65 to 5.21) more likely to carry the diagnosis of angina (p < 0.0001). Results from invasive hemodynamic monitoring were available in approximately 70% of the cases (Table 2). Patients with sarcoidosis more often displayed evidence of pulmonary hypertension. The mean pulmonary artery pressure was approximately 35% higher in patients with sarcoidosis. In patients with sarcoidosis, the mean pulmonary artery pressure was 34.4 ± 13.1 mm Hg, while it was only 25.6 ± 10.2 mm Hg in patients with IPF (p < 0.0001). The cardiac index was similar in the two populations (2.7 L/min/m2 in patients with sarcoidosis vs 2.8 L/min/m2 in patients with IPF). Despite the highly significant differences in pulmonary artery pressures, the pulmonary capillary wedge pressure only differed mildly between the two groups. For the vast majority of patients, the pulmonary capillary wedge pressure was normal. More specifically, the mean pulmonary capillary wedge pressure was 10.3 ± 5.3 mm Hg in patients with sarcoidosis as compared to 10.0 ± 5.6 mm Hg in patients with IPF (p = NS).

Recurrent pulmonary infection necessitating treatment with IV antibiotics was 1.85 (95% CI, 1.14 to 2.99) times more frequent in patients with sarcoidosis. Despite this, the overall utilization of repeated IV antibiotic therapy was low in both cohorts (5.6% for the sarcoidosis group vs 3.1% for the IPF group; p = 0.011). However, the need for continual corticosteroid treatment was common among individuals with both sarcoidosis and IPF. For IPF, 54.9% of patients were reported to be corticosteroid dependent as compared to 55.3% of patients with sarcoidosis (p = NS).

During the time period of study, 131 patients with sarcoidosis underwent OLT compared to 788 individuals with IPF. This disparity in OLT rates (30.8%...
for sarcoidosis vs 37.3% for IPF) was statistically different ($p = 0.0102$). The odds ratio for undergoing OLT if a patient had IPF rather than sarcoidosis was 1.34 (95% CI, 1.07 to 1.68). The probability of OLT as a function of time in the 2 years after being listed with UNOS is shown in Figure 1. The divergence in the rates of transplantation became statistically different by day 182 and remained so thereafter. For patients who did undergo OLT, the median time spent on the list for patients with sarcoidosis was also longer than the interval between listing and OLT for patients with IPF. For patients with sarcoidosis, the median waiting time was 803 days (95% CI, 700 to 1,105 days) as compared to 555 days (95% CI, 513 to 583 days) in patients with IPF.

With respect to mortality after listing, there was no difference based on underlying diagnosis. Approximately, 28% of subjects with sarcoidosis died awaiting OLT. The death rate for patients with IPF was similar (31.1%; $p = NS$). Kaplan-Meier survival curves (Fig 2) also failed to reveal a difference in mortality over time or time to death as a function of the etiology of the end-stage lung disease. In other words, patients with sarcoidosis not receiving OLT fared as poorly on the transplant list as did patients with IPF.

**DISCUSSION**

This large, retrospective study of patients with sarcoidosis and IPF listed for OLT demonstrates that patients with sarcoidosis are at as high a risk for mortality as patients with IPF. Nonetheless, patients with sarcoidosis are less likely to undergo OLT. Moreover, even if they are fortunate enough to receive a lung allograft, patients with sarcoidosis spend a significantly greater time waiting for transplantation.

The present 90-day credit given to persons with IPF listed for OLT does not sufficiently account for this disparity. Specifically, the difference in median waiting times between the two cohorts well exceeds 90 days. Additionally, there is a 117-day difference between the lower limit of the 95% CI for time to transplantation among patients with sarcoidosis (700 days) and the upper limit of the 95% CI for patients with IPF (583 days).

The similarity in mortality rates for these diseases is concerning and difficult to explain. One possibility is that the subjects with sarcoidosis have worse lung function when listed for OLT. Although both the FVC and FEV$_1$ were statistically lower in the sarcoidosis group, the extent of the differences we noted is of unclear clinical significance. Two factors also suggest that reasons other than pulmonary function account for the differential death rates. First, the patients with sarcoidosis required less supplemental oxygen than patients with IPF. Second, there was no difference in functional abilities measured by either 6-min walk distance or by performance status. Alternatively, since patients with IPF who underwent OLT received transplants sooner than patients with sarcoidosis, the mortality in the IPF cohort might have been worse had waiting times been comparable. An element of human bias may also be involved since the patients with sarcoidosis were predominantly female African Americans; however, we have no direct evidence on this point.

The distribution of vascular diseases in the study patients also fails to explicate the lack of a difference in mortality. The overall incidence of any of the comorbidities studied was low. This reflects both the demographics of the population (both groups tended to be young) and the fact that patients with complex medical problems are denied OLT. In other words, patients listed for OLT are “relatively” healthy and are often required to be free of medical illnesses that might limit life expectancy. More importantly, the patients with IPF were more likely to have angina requiring medical therapy. Logically, one would assume that this would lead to excess mortality in those with IPF. This, however, was not observed.

A notable finding of our study was that patients with sarcoidosis had higher mean pulmonary artery pressures than patients with IPF. Pulmonary hyper-
tension is a poor prognostic marker in a number of diseases, and this may contribute to the high mortality faced by patients with sarcoidosis awaiting OLT. Sarcoidosis does not directly involve the pulmonary vessels, as do either primary pulmonary hypertension or some collagen vascular diseases. Likewise, the normal pulmonary capillary wedge pressures in the vast majority of patients indicates that left ventricular failure is not a contributing factor. Therefore the mechanism of pulmonary hypertension in these patients with end-stage lung disease most probably is related to progressive fibrosis and hypoxemia. Again, though, the nearly identical spirometry for the two groups demonstrates that either other issues are involved or that patients with sarcoidosis may be relatively predisposed to the development of pulmonary hypertension.

Irrespective of the etiology for pulmonary hypertension in patients with sarcoidosis, our observations suggest that clinicians must be vigilant in their approach to patients with end-stage sarcoidosis. First, for patients with end-stage disease, screening echocardiography to assess pulmonary pressures may be helpful. With evidence of pulmonary hypertension, physicians may choose to refer subjects with sarcoidosis for OLT sooner than they would have otherwise. Second, hypoxemia should be treated aggressively in this population. Since pulmonary hypertension adversely affects outcome and since treatment of hypoxemia is one of the few interventions available to prevent the progression of pulmonary hypertension, those with advanced sarcoidosis should be thoroughly evaluated for this condition. As a corollary, one possible reason for the disproportionate incidence of pulmonary hypertension in sarcoidosis was that these persons were receiving inadequate supplemental oxygen. Third, rather than wait for lung function to deteriorate to the point that spirometry (either FVC or FEV\textsubscript{1}) reveals values at the near 40% of predicted level, as the mean values did in this study, one should consider offering OLT to patients with sarcoidosis earlier. Fourth, therapies for pulmonary hypertension in sarcoidosis are needed. A small series of three patients suggests that IV prostacyclin may be helpful in pulmonary hypertension associated with sarcoidosis. Furthermore, effort in this area is clearly warranted.

The role for corticosteroids as treatment differentiates sarcoidosis from IPF. Generally, corticosteroids are thought to be beneficial in patients with sarcoidosis, while their value in patients with IPF is less clear. Although the prospective, randomized trials of corticosteroids for sarcoidosis have had limitations, many would agree that the weight of the evidence demonstrates that these agents have some efficacy. For IPF, however, randomized trials are lacking, and the results of observational studies suggest that corticosteroids offer little for the majority of patients with IPF. Inadequate treatment of inflammation, therefore, may in part account for why subjects with sarcoidosis awaiting OLT face significant mortality. In other words, physicians may not be addressing active inflammation in the population with sarcoidosis. Slightly more than one half of patients with sarcoidosis were considered to be corticosteroid dependent and required daily therapy, indicating that corticosteroid were employed frequently. The absence of data regarding total dose of corticosteroids, duration of treatment, serum inflammatory markers, and concomitant use of other agents such as methotrexate, though, make it difficult to address the issue of untreated inflammation. In short, our data cannot conclusively speak to this question.

Our study has several limitations. First, its retrospective nature exposes it to certain types of bias. Unlike most retrospective projects, the UNOS database consists of information recorded concurrently with listing for OLT rather than data abstracted purely post hoc. Therefore, recall bias is unlikely to be a significant concern. Additionally, UNOS remains dependent on the referring transplant centers for the quality of the data, as opposed to a database supervised by a single institution. UNOS also did not have information regarding either diffusion capacity of the lung for carbon monoxide or the FEV\textsubscript{1}/FVC ratio. Second, we only focused on those actually listed for OLT. No information is available for patients deemed ineligible for OLT, and our results may not be generalizable to that population. Put simply, referral bias may have affected our observations. Because IPF follows an insidiously progressive course while the natural history of sarcoidosis is more variable, clinicians may tend not to refer patients with sarcoidosis for OLT until they are relatively more ill. In other words, our findings may reflect the fact that physicians may be prone to delay listing for patients with sarcoidosis, expecting the disease trajectory to plateau. Third, the UNOS database had no information on health insurance, educational, or socioeconomic status. Each of these affects outcomes in health care and may play a role in outcomes for patients listed for OLT. Fourth, the proportional number of patients with sarcoidosis awaiting OLT is small. Specifically, they comprised <4% of the entire data set. Nonetheless, the absolute number was relatively large for studies of patients with end-stage sarcoidosis, and we were still able to find many highly significant differences between the cohorts. Similarly, the range in the CIs for the odds ratios we computed when comparing IPF

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and sarcoidosis patients were narrow, suggesting that we had adequate power to focus on many important issues.

In summary, patients with sarcoidosis listed for OLT spend significantly longer waiting for an allograft than do patients with IPF. This difference cannot solely be explained by the waiting-time credit given to patients with IPF. Despite the disparity in transplantation rates, patients with sarcoidosis are as likely as patients with IPF to die while listed. The presence of pulmonary hypertension in advanced sarcoidosis is concerning. Therefore, physicians caring for patients with end-stage sarcoidosis should consider screening for this process.

REFERENCES