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Bronchiolitis obliterans syndrome and survival following lung transplantation for patients with sarcoidosis

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Abstract. *Background:* End-stage sarcoidosis is characterized by severe pulmonary fibrosis and is often poorly responsive to medical therapy. Lung transplantation, therefore, may be the only treatment option. Currently, there are few studies evaluating long-term outcomes following transplantation for these patients. Our aim was to evaluate post-transplant morbidity and survival of patients with sarcoid compared to recipients transplanted for idiopathic pulmonary fibrosis (IPF). *Methods*: We retrospectively examined 300 lung transplant recipients using a dedicated database. Over a 10-year period, 15 (5.0%) patients with sarcoidosis and 48 (16%) patients with IPF were identified. Primary outcome measures included rate and time to onset of bronchiolitis obliterans syndrome (BOS) and survival. *Results*: Recipients in the sarcoid group were younger and predominantly female compared to recipients in the IPF group. Five of 15 (33%) sarcoid patients developed BOS versus 15 of 48 (31%) IPF patients (p=1.0). There was no significant difference in the time to BOS onset. Median survival was 1,365 days for the sarcoid group and 1,593 days for the IPF group (Hazard Ratio 0.94 by Kaplan-Meier analysis; [95% CI] 0.33-2.67; p = 0.90). *Conclusions*: We observe similar long term outcomes following lung transplantation for sarcoid and IPF recipients. Transplantation remains a treatment option for end-stage sarcoidosis, as BOS and survival rates are comparable to IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2008; 25: 117-124)*

Key words: sarcoidosis, lung transplantation, bronchiolitis obliterans syndrome, BOS, idiopathic pulmonary fibrosis; IPF

Abbreviations:

BOS	bronchiolitis obliterans syndrome
CI	confidence interval
CMV	cytomegalovirus
CsA	cyclosporine
CXR	chest radiograph
DLCO	diffusing capacity for carbon monoxide
FEV_1	forced expiratory volume, 1 second
FVC	forced vital capacity
IPF	idiopathic pulmonary fibrosis
ISHLT	International Society of Heart and Lung Transplantation
IL	interleukin
ng/ml	nanograms per milliliter
pCO_2	partial pressure carbon dioxide (mmHg)
pO_2	partial pressure oxygen (mmHg)
TBB	transbronchial biopsy
OPTN	Organ Procurement and Transplantation Network

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Introduction

Sarcoidosis, a multisystem disease of unknown etiology, predominately affecting the lungs and intrathoracic lymph nodes (1), is typically characterized by the development of non-necrotizing granulomas in affected organs. While some patients remain asymptomatic, approximately one-third may develop chronic pulmonary disease, including progression to end-stage disease with parenchymal fibrosis and scarring (2). As fibrosis advances, the pathophysiology and clinical course of sarcoidosis closely mimics that of idiopathic pulmonary fibrosis (IPF). Medical therapy for patients in the later stages of either condition is generally ineffective.

Lung transplantation is one potential treatment option for patients with end-stage sarcoidosis. While transplantation is an accepted approach for several chronic respiratory diseases, its benefit in sarcoidosis remains uncertain. This is, in part, due to the multi-system nature of this disorder and the risk of recurrence in the transplanted organ. Furthermore, because the histopathology of sarcoidosis and IPF differ, important differences in post-transplant outcomes may be observed. Unfortunately, the mortality rates for patients awaiting lung transplantation, with either sarcoidosis or IPF, are similar (28.1% and 31.1%, respectively) (3).

Earlier studies have observed no difference in 30-day mortality following lung transplantation for sarcoidosis when compared with other transplant indications (4). Another study evaluating 12 sarcoid subjects found 3 and 5-year survival rates of 70% and 56%, respectively, which were comparable to their overall post-transplant survival rates (5). There are few studies, however, examining longer-term outcomes, particularly rates of bronchiolitis obliterans syndrome (BOS), in sarcoid patients following lung transplantation. BOS is thought to correlate with chronic allograft rejection and typically manifests as a progressive obstructive ventilatory defect. While potential recipients are usually without clinically evident extra-pulmonary disease, it is unclear whether immunosuppression affects the occurrence of systemic disease post-transplant or impacts survival. We hypothesized that, due to differences in the natural history and pathophysiology of sarcoid and IPF, there may also be differences in outcomes following lung transplantation. The purpose of this study was to evaluate BOS and survival rates of patients with sarcoidosis, compared to recipients who underwent lung transplantation for IPF, at a single tertiary care center. Secondary outcomes included rates and severity of acute rejection.

Methods

Subjects

A retrospective review of lung transplant recipients over a 10-year period (1994-2004) at a tertiary care center was performed utilizing a dedicated transplant database and record review. During this period, 300 patients underwent lung transplantation. Of these, 15 patients (5.0%) had sarcoidosis and 48 (16%) had IPF. Year of transplant for the 15 sarcoid recipients was: 1995-97, n=3; 1999, n=3; 2000-01, n=5; and 2002, n=4. A diagnosis of sarcoidosis or IPF was established pre-operatively using available clinical, radiographic, and histological data. The primary endpoints of this study were BOS and survival following lung transplantation. The frequency and severity of acute rejection episodes comprised a secondary endpoint. Controls were contemporaneous to time of transplant to minimize the effect of therapeutic advances on recipient morbidity and mortality. Waiver of informed consent was granted and the study was approved by the Institutional Review Board of the University of Alabama at Birmingham.

Study Variables

Enrollment data included basic demographics and clinical parameters, pre- and post-transplantation. Donor factors that may influence transplant outcome, including demographics and cold-ischemia time, were also noted. Time and cause of death were recorded for patients who died following transplantation. When possible, the listed cause of death was compared to autopsy findings.

Immunosuppression

The initial immunosuppressive regimen from 1994-2002 consisted of cyclosporine (CsA), azathioprine, and prednisone. Beginning in June 2002, the initial regimen was modified to tacrolimus, my-

cophenolate mofetil, and prednisone. All patients underwent routine laboratory testing to monitor for medication-related side-effects. Starting in 2001, patients also received an IL-2 receptor antibody (daclizumab or basiliximab) as part of induction immunosuppression. Additional details on immunosuppression are provided as a supplement.

Acute Rejection and Bronchiolitis Obliterans Syndrome

Surveillance fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) was performed after transplant or when clinically indicated for suspected infection or rejection. Acute cellular rejection was diagnosed if TBB revealed grade A2 or higher findings, as defined by the ISHLT scale (6). Acute rejection was also diagnosed, in the absence of TBB, when clinical suspicion warranted treatment with high dose corticosteroids. Unless otherwise stated, spirometric parameters were referenced to the predicted values of the recipients.

Spirometric evaluation for BOS was based on change in FEV_1 according to ISHLT diagnostic criteria (7). Additionally, patients with suspected BOS underwent TBB or surgical lung biopsy to exclude alternative diagnoses that might result in airflow loss. Treatment of BOS was standardized and consisted of altered or augmented immunosuppression, administration of lympholytic (anti-thymocyte) therapy, and/or photopheresis therapy (8).

Statistical Analysis

Descriptive statistics, such as means and standard deviations for continuous variables and frequencies and proportions for categorical variables, were computed for all study variables of interest. Baseline characteristics and outcome measures were compared using the two-group t test or the Wilcoxon rank-sum test (as needed) for quantitative variables and Fisher's exact test for categorical variables. Exact 95% confidence limits were computed for the odds ratios. Estimates of time to BOS and time to death were computed using Kaplan-Meier survival statistics. Univariate comparisons of these time-to-event outcomes were performed using the log-rank test, and multivariate comparisons were performed using Cox proportional hazards models. All Cox regression models included patient cohort (sarcoidosis and IPF) and were adjusted for age, gender, and race. Measures of pulmonary function such as FVC and FEV_1 were not included in these models as these measures were obtained pre-transplant. All statistical tests were two-sided and were performed using a type I error rate of 0.05. Analyses were performed using GraphPad (version 4.0; GraphPad Software, Inc., San Diego, CA) and SAS (version 9.1.3; SAS Institute, Inc., Cary, NC).

Results

Patient Characteristics

Clinical characteristics of the 15 sarcoid patients and 48 IPF patients who underwent lung transplantation are shown in Table 1. Sarcoid recipients were more often younger (42.6 vs. 55.8 years), female (80% vs. 41.7%), and African-American (73.3% vs. 14.6%), compared to IPF recipients ($p<0.01$). Mean absolute FVC and FEV_1 were 1.28±0.42 L and 0.97±0.32 L for sarcoid patients, and were 1.92±0.68 L and 1.59±0.49 L for IPF patients ($p<0.01$). However, there were no significant differences between groups in % DLCO, pO_2, pCO_2, 6-minute walk distance, mean pulmonary arterial pressure, or donor/recipient CMV serologies.

Sarcoid recipients more commonly had pre-transplant chest radiographs that were characterized by the presence of bullae with fibrosis, compared to IPF recipients (53.3% vs. 0%, $p<0.001$). However, only 1 sarcoid recipient had a mycetoma, noted 30 months before transplant and treated by right upper lobectomy. No significant difference in donor characteristics between recipient groups was noted.

Acute Rejection

Eight of 15 (53.3%) sarcoid recipients had grade A2 or higher acute rejection by TBB within 1 year of transplant, compared to 29 of 48 (60.4%) IPF recipients ($p=0.76$). Another 2 (13.3%) sarcoid recipients and 6 (12.5%) IPF recipients were treated for acute rejection symptoms, in the absence of confirmatory biopsy. There was no significant difference between groups in the frequency of grade 3 or higher acute rejection.

Table 1. Characteristics at Transplantation*

	Sarcoidosis n=15	IPF n=48	p Value
Demographics			
Mean Age (Years)	42.6±9.4	55.8±7.9	<0.001
Female (n, %)	12.0 (80.0)	20.0 (41.7)	<0.001
African-American (n, %)	11.0 (73.3)	7.0 (14.6)	<0.001
Pulmonary Function			
FVC (% predicted)	34.7±13.8	47.8±14.5	<0.01
FEV_1 (% predicted)	33.9±13.1	52.7±15.6	<0.001
DLCO (% predicted)	25.4±13.4	27.7±12.7	ns
pCO_2 (mmHg)	42.4±4.7	40.7±5.4	ns
pO_2 (mmHg)	68.0±12.1	62.1±15.0	ns
Supplemental O_2 (L/min)	2.0±0.9	2.8±2.1	ns
6-Min Walk (Feet)	983±316	1115±425	ns
Transplant			
Single	13	47	ns
Bilateral	2	1	
Hemodynamics			
PA Systolic (mmHg)	47.2±16.2	39.8±15.2	ns
PA Diastolic (mmHg)	18.8±5.9	16.5±7.6	ns
PA Mean (mmHg)	31.9±11.1	26.3±10.8	ns
Cardiac Index ($L/min/m^2$)	3.1±0.9	2.8±0.5	ns
PVR ($dynes/sec/cm^5$)	333±176	240±152	ns
CMV Serology (D/R)			
+/+	6	29	ns
+/-	2	4	ns
-/+	6	14	ns
-/-	1	1	ns
Donor Characteristics			
Mean Age (Years)	28.6±13.5	27.6±11.2	ns
Cold-Ischemia Time (min)	233±78	249±64	ns
Female (%)	33.3	25.0	ns
African-American (%)	26.7	22.9	ns

* Values are presented as means ± standard deviations or percentages, as indicated. FVC, forced vital capacity. FEV_1, forced expiratory volume, 1 second. DLCO, diffusing capacity of lung. pCO_2, partial pressure carbon dioxide. pO_2, partial pressure oxygen. PA, pulmonary artery. PVR, pulmonary vascular resistance. ns, non-significant.

Occurrence of Bronchiolitis Obliterans Syndrome

Table 2 shows the number of transplant recipients in both sarcoid and IPF groups who were diagnosed with BOS. Five of 15 (33.3%) patients in the sarcoid group and 15 of 48 (31.2%) patients in the IPF group developed BOS (OR 0.91, 95% CI 0.23-4.01, p=1.0). At the time of diagnosis, there was no significant difference in BOS grade between groups: in the sarcoid group, 2 of 5 (40%) were grade 0-p and 3 of 5 (60%) were grade 1; in the IPF group, 5 of 15 (33%) were grade 0-p, 7 of 15 (47%) were grade 1, and 3 of 15 (20%) were grade 2 (p=ns for corresponding BOS grades). Mean FEV_1 at BOS diagnosis was 1.14 L (range, 0.91-1.55) in the sarcoid group and 1.56 L (range, 0.96-2.54) in the IPF group (p=0.052).

Figure 1 displays the number patients in both the sarcoid and IPF groups who remained free from BOS over time. Table 3a demonstrates the Cox proportional hazards model for BOS, adjusted for age, gender, and race. Mean time to BOS diagnosis was 23.9±27.4 months for the sarcoid recipients and 22.3±20.8 months for the IPF recipients. There was a trend toward earlier BOS occurrence in IPF versus sarcoid recipients by Cox proportional modeling (Hazard Ratio 3.47; 95% CI: 0.93-12.9; p=0.06).

Table 2. Bronchiolitis Obliterans Syndrome and Death following Lung Transplantation*

	Sarcoidosis n=15	IPF n=48	OR	95% CI
BOS	5 (33.3)	15 (31.2)	0.91	0.23-4.01
Death	8 (57.1)	24 (50.0)	0.88	0.23-3.27

* Data are presented as No. (%). IPF -idiopathic pulmonary fibrosis; BOS -bronchiolitis obliterans syndrome. OR -odds ratio

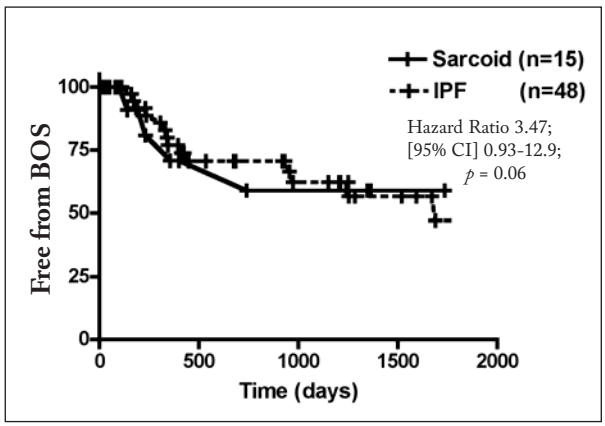

Fig. 1. Freedom from Bronchiolitis Obliterans Syndrome after Transplant for Sarcoid and IPF Recipients

Survival

Figure 2 demonstrates survival characteristics for sarcoid and IPF groups. Table 3b demonstrates the Cox proportional hazards model for survival, adjusted for age, gender, and race. Sarcoid and IPF recipients were followed over a mean of 46±34 and 45±36 months, respectively. Median survival for the

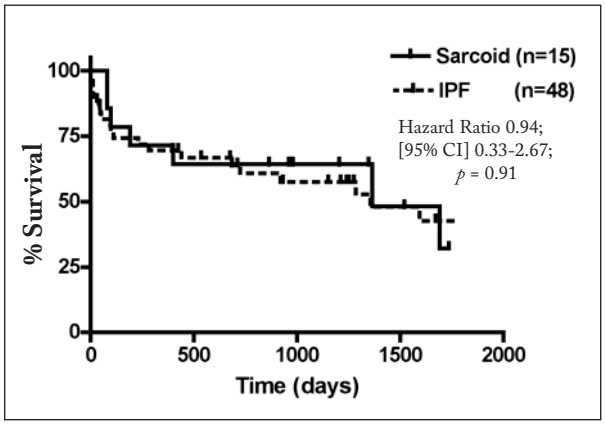

Fig. 2. Survival Following Lung Transplantation for Sarcoid and IPF Recipients

sarcoid group was 45.5 months (3.7 years) and 53.1 months (4.4 years) for the IPF group. Mean survival at 3, 12, 36, and 60 months for sarcoid recipients was 86.7%, 80%, 66.7%, and 46.7%, respectively. Mean survival for IPF recipients at the same time intervals was 83.3%, 75%, 72.9%, and 58.3%. There was no difference in survival between recipient groups (Hazard Ratio 0.94; 95% CI: 0.33-2.67; p=0.91).

There were no significant differences in cause of death following transplantation between groups. Of the 8 patients who died following transplantation for sarcoidosis, cause of death was listed as BOS (n=3), infection (n=3), and hemoptysis (n=2). For the IPF recipients who died, the most common causes of death included infection (n=6), complications from BOS (n=5), primary graft dysfunction (n=4), multiple organ failure (n=3), airway dehiscence (n=2), and malignancy (n=1).

Table 3. Cox Proportional Hazards Models

Variable	Referent Group	Estimate±SE	Hazard Ratio (95% CI)	P Value
a. Cox Proportional Hazards Model with Time to BOS as the Dependent Variable and Diagnosis Group, Age, Gender, and Race as Independent Variables				
Diagnosis Group	Sarcoid	1.24±0.67	3.47 (0.93,12.92)	0.06
Age	—	-0.03±0.03	0.98 (0.93,1.03)	0.35
Gender	Male	0.10±0.52	1.11 (0.40,3.09)	0.85
Race	Caucasian	1.40±0.61	4.06 (1.23,13.44)	0.02
b. Cox Proportional Hazards Model with Time to Death or End as the Dependent Variable and Diagnosis Group, Age, Gender, and Race as Independent Variables				
Diagnosis Group	Sarcoid	-0.06±0.53	0.94 (0.33,2.67)	0.91
Age	—	0.02±0.03	1.02 (0.97,1.07)	0.50
Gender	Male	-0.07±0.40	0.93 (0.43, 2.02)	0.85
Race	Caucasian	0.67±0.53	1.95 (0.69, 5.54)	0.21

Discussion

This study demonstrates that long-term outcomes for patients with sarcoidosis following lung transplantation, particularly with regard to BOS and survival rates, are comparable to transplant outcomes for patients with IPF. These are notable findings, as few studies have reported survival rates for sarcoid transplant recipients, and fewer still have utilized a control population (5, 9, 10).

This is the first reported study to compare BOS rates in sarcoid recipients with a uniform population of IPF recipients. It has been postulated that patients transplanted for sarcoidosis may have higher rates of BOS compared to patients transplanted for other indications. This is in part related to similarities in basic immunologic mechanisms observed in both conditions, including elevated chemokine/cytokine stimulation and $CD4^+$ lymphocyte/macrophage activation (11, 12). However, this study did not detect a higher BOS rate compared to a cohort of IPF recipients; in fact, we observed a trend toward earlier BOS development in our IPF cohort after adjusting for age, race, and gender effects. These findings may be due to the selection of sarcoid patients with less systemic involvement for transplantation, effects of immunosuppression on mechanisms of disease, or similarities in post-transplant BOS screening for all transplant recipients. As the pathogenesis of BOS and sarcoidosis are better characterized, therapeutics directed against specific components of the innate and humoral immunity pathways may alter the natural history of each disorder.

Table 4 summarizes the key findings of recent studies following lung transplantation for sarcoidosis. Aside from the current study, only Nunley et al. (10) utilized a control group, consisting of COPD and ILD recipients. Race is not reported except in Milman et al. (13), where transplant recipients were all Caucasian. The primary aim of the Arcasoy et al. (14) study was to identify factors predictive of death for patients with sarcoidosis listed for transplantation; however, survival was reported for patients who underwent transplantation. While these prior studies evaluate some aspects of the post-transplant course of sarcoid patients, our study extends the follow-up period and details factors that may contribute to morbidity and survival in this patient population.

Whether sarcoid recipients have comparable outcomes following single or bilateral lung transplantation is unresolved. Several variables, such as the presence of extensive bullous disease, mycetoma, or pulmonary hypertension, influence the choice of transplant procedure; however, there may be additional unrecognized factors important to procedure selection. The majority of sarcoid patients in our series underwent single lung transplantation with similar short and long-term outcomes as IPF recipients. Therefore, in the absence of obvious factors that warrant bilateral transplantation, our results support a continued role for single lung transplantation in end-stage sarcoidosis.

Our sarcoid population was predominately African-American and female. While it is difficult to generalize our results to all sarcoid recipients, this population reflects our regional distribution of sarcoidosis patients. The incidence of sarcoidosis is notably higher in African-Americans compared to Caucasians (2, 3), and African-Americans are typically affected more acutely and severely than people of other races (15). Although our Cox model suggests that African Americans may develop earlier BOS compared to Caucasians when controlled for age, gender, and diagnosis, this model did not in-

Table 4. Outcome following Lung Transplantation for Sarcoidosis: Summary of Recent Studies*

Study	N	Age	Gender	Race	Transplant	BOS N (%)	% Survival (1;3;5 yr)
Walker 1998	12	46.5	9-M;3-F	-	10-S;2-B	3 (25%)	- ; 70 ; 56
Nunley 1999	9	44.4	2-M;7-F	-	9-S	4 (50%)	67; ~55; -
Milman 2005	7	51†	5-M;2-F	7-C	7-S	6 (86%)	100; - ; -
Arcasoy 2005	12	-	-	-	4-S;8-B	-	62; 50; -
Current Study	15	42.6	2-M;13-F	13-AA	13-S;2-B	8 (57%)	80; 67; 47

* Mean age is reported for all values except †, which denotes median value. M=male; F=female; C=Caucasian; AA=African-American; S=single. B=bilateral; BOS-bronchiolitis obliterans syndrome; "-" denotes where data are not reported.

clude other variables associated with BOS development, like acute rejection episodes, respiratory viral infections, or the presence of gastroesophageal reflux. Prior to concluding that race influences timing of BOS, this observation should be re-evaluated in a larger study using models that incorporate such variables. The post-transplant course of sarcoid patients in this study, however, did not significantly differ from the IPF cohort, the majority of which were Caucasian. Furthermore, while a previous study (4) has reported higher 30-day mortality in African-American sarcoid recipients, we did not observe this finding in our own cohort.

This study has certain limitations. First, this study reflects a single center experience and may, in part, be biased by the clinical practices of the center. While mortality data following lung transplantation is available from the Organ Procurement and Transplantation Network (OPTN), acute rejection episodes and BOS rates are not presently collected. Second, because BOS is a clinical diagnosis and may mimic other post-transplant complications, there may be more variability in defining actual BOS onset. However, the diagnostic approach to BOS was the same for both groups and performed in a systematic manner. Third, the number of patients with sarcoidosis described in this study is small. Although only 15 sarcoid recipients are presented, this cohort comprises 5% of our transplant population, compared to about 2.5% nationally, and encompasses one center's experience over a 10-year period. Recognizing that our study is underpowered, we have performed a post hoc power calculation based on the two-sided two-group chi-square test, a significance level of 5%, a difference of 15% between sarcoidosis and IPF (assuming that one of these proportions is 50% and the other is 35%), and 80% power. A total of 170 patients per group would be needed to detect a mortality difference of 15% between groups as being statistically significant. Data reported herein are derived from a prospectively maintained, dedicated transplant database, thereby reducing the risk of bias. Still, the retrospective nature of the study makes it possible that specific outcome measures were missed in some patients.

In summary, our results suggest comparable rates of BOS and survival for transplant recipients with sarcoidosis and IPF. Acute rejection episodes occur with similar frequency in both groups. These findings, however, should be confirmed through a larger, multi-center collaborative investigation. Given the high mortality rate of sarcoid patients awaiting transplantation, early transplant referral for medically refractory disease is important. With satisfactory outcomes, lung transplantation should remain a viable option for patients with sarcoidosis and end-stage pulmonary disease.

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Supplement

UAB Immunosuppressive Regimen for Lung Transplantation

The initial immunosuppressive regimen from 1994-2002 consisted of cyclosporine (CsA) administered starting at a dose of 0.5-1 mg/kg orally twice daily and adjusted according to measured CsA trough levels; azathioprine starting at a dose of 2-4 mg/kg and adjusted as tolerated; and prednisone, which was tapered following transplantation to a maintenance dose of 5-10 mg daily. CsA levels were monitored routinely to maintain levels at 350-400 ng/mL for the first 6 months after transplantation, 300-350 ng/mL for months 6-24, and 150-200 ng/mL beyond 24 months.

Beginning in June 2002, the initial immunosuppressive regimen was modified to tacrolimus starting at 0.04 mg/kg orally twice daily, mycophenolate mofetil starting at 500 mg orally bid, and prednisone. Tacrolimus levels were monitored routinely to maintain levels at a range of 12-15 ng/mL for the first 6 months post transplant, 10-12 ng/mL for months 6-24, and 8-10 ng/mL beyond 24 months. The dose of mycophenolate mofetil was increased as tolerated up to 3000 mg daily.