

Vascular Sclerosis and the Rate of Bronchiolitis Obliterans Syndrome in Lung Transplantation Patients

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A. Study Purpose and Rationale

Lung Transplantation is a therapeutic option for many different lung diseases. Despite the longer survival and improved quality of life that transplantation can offer a patient, there are many complications that limit the long-term preservation of the graft's function and the patient's survival. The most pervasive problem after lung transplantation is chronic rejection, otherwise known as bronchiolitis obliterans (BO). It is characterized histologically by fibroproliferation that targets small airways, leading to submucosal fibrosis and luminal obliteration.¹ Because histological diagnosis is unreliable, with a sensitivity of only 17%,² the diagnosis is made physiologically with Pulmonary Function Testing (PFTs), thus making it a physiologic entity known as bronchiolitis obliterans syndrome (BOS). PFTs must demonstrate a sustained drop in Forced Expiratory Volume in 1 second (FEV₁) to 80% or less of the patient's peak value after transplantation.³ While uncommon in the first few months after transplantation, BOS becomes progressively more likely as patients survive further beyond the time of transplantation, reaching upwards of 60-70% of patients who survive for 5 years.⁴ In a Stanford University cohort of 61 transplant patients, rates of freedom from BOS at 1, 3, and 5 years post-transplantation were 67%, 42%, and 15%, respectively.⁵ In theory, every lung transplant patient ultimately progresses to BOS, unless they succumb to other complications prior to its development. The mortality rate of BOS has been quoted to be approximately 40% within 2 years of diagnosis.⁶ With such a prevalent and debilitating complication occurring in so many transplant recipients, it is important to determine any factors that may cause or be associated with BOS, in the hopes that new treatment modalities can be designed to counteract those factors and delay the progression to BOS. Currently, there are 3 accepted risk factors for BOS, which are acute rejection, lymphocytic bronchitis/bronchiolitis, and CMV pneumonitis. Other potential/hypothetical risk factors are infection, organizing pneumonia, donor age, recipient age, graft ischemic time (time between taking the organ from the donor and transplanting it into the recipient), and HLA-mismatching.⁷

As part of each transplant recipient's routine surveillance for acute and chronic rejection, he or she is monitored with frequent bronchoscopies with transbronchial biopsies as part of their post-transplant care (looking for evidence of acute rejection), as well as routine PFTs to assess for BOS. Many of the aforementioned risk factors for BOS, particularly the three accepted risk factors, can be identified on the biopsy specimen. Likewise, there are several incidental findings seen on biopsy that are of undetermined significance, and may be markers for other potential causes of chronic rejection. One such histological finding is vascular sclerosis. There is very little known or written about vascular sclerosis in the transplant literature. According to transplant physicians at CUMC, it occurs with a frequency of approximately 10% of all transplant recipients. It is easily identified on pathological evaluation with routine stains, and is characterized by thickening and fibrosis of the vessel walls. Because it is seen with a fair amount of frequency, we propose to compare patients with vascular sclerosis on biopsy within the first year after transplantation with those who have no findings of vascular sclerosis, and compare the time elapsed until the development of BOS. Our hypothesis is that vascular sclerosis, as a potential marker for risk factors for chronic rejection, will result in a shorter time to development of BOS.

B. Methods

Study Design:

This will be a prospective multi-center cohort study of subjects undergoing lung transplantation at the 10 busiest transplantation centers in the United States (CUMC, University of Pennsylvania, University of Pittsburgh Medical Center, Cleveland Clinic, Duke University Medical Center, Barnes Jewish Hospital, UCLA Medical Center, University of Minnesota Medical Center, University of Michigan Medical

Center, and University of Florida). Patients will be enrolled over a 3 year period (2008-2010), with a minimum of 3 years of follow-up per patient (end date 2013). With each center performing, on average, 60 transplantations per year, there will be approximately 1800 subjects available for analysis (power analysis discussed below). All data being obtained from each subject in this study is data that is already routinely collected as part of every post-transplantation patient's standard clinical care, and the patient's enrollment in the study will have no impact on the course of his/her clinical care. For each subject, baseline demographics will be obtained from the subject's medical record. After transplantation, subjects will undergo routine bronchoscopy with transbronchial biopsies as part of their clinical management, whose frequency may vary from institution to institution. No additional bronchoscopies or biopsies will be performed for the sake of the study. We will obtain the biopsy results of each subject and make note of all biopsies within the first year that demonstrate vascular sclerosis (VS) as determined by each institution's respective pathology department. All of those subjects who have VS will form the 'experimental group' and all those who have no evidence of VS will form the 'control group.' All subjects will be followed at their respective institutions as per each institution's standard management of transplantation patients, and all PFT results (tests done routinely in the course of a transplant recipient's care) through 2013 (allowing for a minimum of 3 years of data for every patient) will be collected in order to document the occurrence of BOS. No additional PFTs will be performed for the sake of the study. There will be no crossover between the two groups. The primary outcome in this study is mean time to development of BOS, or BOS-free survival time.

We will be applying for a Research Project Grant (R-01) from the NIH for funding of this study. After approval by each institution's respective institutional review board, we will coordinate with the other centers for the enrollment of patients and collection of all data necessary for the study.

Power Analysis:

This is a comparison of two groups in the mean time to development of BOS, and thus requires survival analysis. Assuming a median BOS-free survival time of 4 years in the control group, we would need 180 subjects with VS (which means a total of 1800 subjects assuming 10% incidence of VS) to detect a 1 year decrease in BOS-free survival in the VS group (or hazard ratio of 1.37), assuming 80% power and an alpha of 0.05. With that same sample size, we would also be powered to detect a 13 month decrease in survival time (or HR 1.4) if the control group's median BOS-free survival was 4.5 years, or an 11 month decrease in survival time if the control group's median survival were only 3.5 years (or HR 1.35). Using the same sample size, the study is sufficiently powered to detect the same time differences (or hazard ratios) whether the incidence of VS (assumed to be 10%) is anywhere from 5 to 15%.

Statistical Analysis:

Baseline demographics of the two groups will be compared using chi-square test for categorical variables and t-test for continuous variables. Analysis of the primary outcome will be performed with Kaplan-Meier analysis, with log-rank test to compare BOS-free survival between the VS group and the control group. Cox proportional-hazards regression will then be used to analyze the effect vascular sclerosis has on BOS-free survival, which will control for confounding risk factors.

C. Study Procedures

The study procedures being performed on each patient necessary for this study are bronchoscopy with transbronchial biopsy and Pulmonary Function Testing (PFTs). These studies are required as part of each subject's standard clinical management. No bronchoscopies, biopsies, or PFTs will be performed beyond those that are already part of his or her clinical management. Bronchoscopy with biopsy usually requires approximately one-half hour, as do PFTs. No additional catheters or instruments will be required for the sake of this study. The subjects will experience no more pain, discomfort, or inconvenience than that which they would experience as part of their routine post-transplantation care. Each institution has its own protocol for the frequency with which it performs these tests, and this study will not alter the frequency with which they are done as part of standard clinical care. The entire study will last approximately 6 years (3 year enrollment period with a minimum of 3 years of follow-up per subject). Each subject's data will be collected for as long as possible from the time of enrollment through the completion date of the study.

D. Study Drugs

There are no drugs being used in this study.

E. Medical Device

There are no medical devices being used in this study.

F. Study Questionnaires

There are no questionnaires needed for this study.

G. Study Subjects

Inclusion criteria: all patients over the age of 18 who have undergone lung transplantation after January 1 2008 at all of the 10 centers cooperating in this study are eligible to participate.

Exclusion criteria: There are no exclusion criteria so long as they meet the above inclusion criteria. There are no restrictions on gender, race, ethnicity, or language spoken.

H. Recruitment of Subjects

Study subjects will be identified by lung transplantation physicians at their respective transplant centers. Because these are the patients' primary physicians, they will be able to approach the patient, explain the nature of the study, and determine if the patient is willing to allow us to use the data from his post-transplant care for the sake of the study.

I. Confidentiality of Study Data

All study data will be coded so as to eliminate any personal identifiers and all data will be stored in a secure location, accessible only to the investigators.

J. Potential Conflict of Interest

There are no potential conflicts of interest on the part of the investigators, CUMC, or any of the other centers participating in the study.

K. Location of the Study:

The study will be conducted at CUMC, as well as at the University of Pennsylvania, University of Pittsburgh Medical Center, Cleveland Clinic, Duke University Medical Center, Barnes Jewish Hospital, UCLA Medical Center, University of Minnesota Medical Center, University of Michigan Medical Center, and University of Florida. IRB approval will be obtained from all other centers prior to their participation in the study.

L. Potential Risks

There are no risks to subjects beyond the risks already being incurred as part of their ongoing post-transplantation care. No investigational drugs or instruments will be used that pose additional risk.

M. Potential Benefits

There are no immediate benefits to any of the subjects enrolling in the study, but there is the potential long-term benefit of identifying early markers of chronic rejection that may result in modification of therapy for transplant recipients in the future.

N. Alternative Therapies: N/A

O. Compensation to Subjects

No compensation will be provided to participating subjects.

P. Cost to Subjects

There are no additional costs to participating subjects.

Q. Minors as Research Subjects: N/A

R. Radiation or Radioactive Substances: N/A

References

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