ICCR Project Proposal Write-up November 10th, 2009

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1. Study Purpose and Rationale

Title: Outcomes of lung transplantation in idiopathic non-specific interstitial pneumonitis with undifferentiated connective tissue disease

Rationale: Lung transplantation is a valuable therapy for a variety of end-stage lung diseases, with growing evidence supporting prolonged survival after transplantation. However, given the relative scarcity of donor lungs available, it is important to identify transplant candidates who will have favorable long term outcomes and also identify subsets of transplant recipients who do poorly post-transplantation.

One area of controversy regarding poor post-transplant outcomes is in patients with diffuse parenchymal lung disease (DPLD) associated with connective tissues disease (CTD). Although DPLD secondary to CTD was the indication in only 0.5% of lung transplantations in the ISHLT registry between 1995 and 2001[1], there is an evolving suggestion that some patients with idiopathic non-specific interstitial pneumonitis [NSIP] actually also meet criteria for an undifferentiated connective tissue disease [UCTD][2] and may account for a larger proportion of lung transplants performed, particularly as the ISHLT registry does not distinguish the "idiopathic" NSIP subtype from the usual interstitial pneumonitis[UIP] subtype of idiopathic pulmonary fibrosis[IPF]. Although there has been one study[3] in the literature examining lung transplant outcomes in DPLD with confirmed scleroderma (which showed no survival difference), there has been no studies examining transplant outcomes in patients with "idiopathic" NSIP and with features of UCTD. The clinical experience at the transplant program at Columbia raises concern that these NSIP patients with features of UCTD tend to do worse post-transplant. One possible underlying hypothesis is the presence of worse gastroesophageal reflux symptoms in patients with UCTD, which could lead to more aspiration and subsequent infectious events. Another way patients with UCTD might have worse post-transplant outcomes could be their potentially more reactive underlying immune system that might be more likely to reject their transplanted lung despite immunosuppressants?

Ultimately, if patients with idiopathic NSIP also have clinical, serological, radiological or pathological data that meet criteria for an undifferentiated CTD have significantly worse outcomes post-transplant, perhaps the offer of lung transplantation to these patients should be carefully reconsidered.

Null hypothesis: There is no difference in post-lung transplantation outcomes between patients with idiopathic NSIP and UCTD and patients with IPF/UIP.

2. Study Design and Statistical Analysis

Study type and design: A retrospective chart review of the cohort of adult patients who have undergone lung transplantation under the NYP-Columbia Lung Transplant Program from 1999-2007

Inclusion in "Exposed" group: post-lung transplant patients who had pre-transplant diagnosis of idiopathic NSIP and suspected undifferentiated CTD

- pre-transplant diagnosis of idiopathic NSIP: clinical, radiological, pathological diagnosis based on history and physical, chest x-ray, high-resolution CT, PFTs, and lung biopsy.
- suspected undifferentiated CTD, criteria as per Table 1 in reference paper[2]:
  - serologic evidence of systemic inflammation in the absence of clinical infection: at least positive for one of the following: ANA, Rheumatoid factor, anti-scl 70 antibody, anti-SS-A or SS-B, anti-Jo-1, elevated ESR and CRP
  - AND at least one clinical manifestation of potential CTD: arthralgias, GERD, Raynaud's, dysphagia, Sicca symptoms, recurrent fevers, rash, morning stiffness, unintentional weight loss, proximal muscle weakness, oral ulcers, photosensitivity
  - AND does not meet any established American College of Rheumatology criteria[4] for specific connective tissues disease

Excluded: Patients with a defined CTD according to ACR criteria or a known cause for their interstitial lung disease (e.g. drug-induced, hypersensitivity pneumonitis)

Control group: post-lung transplant patients who had pre-transplant clinical, radiological, and pathological diagnosis of idiopathic pulmonary fibrosis (with UIP histology on lung biopsy)

Primary end point: survival
Secondary end points: rate of infections requiring hospitalization per year, rate of rejection episodes (on surveillance biopsies) per year

Potential confounders (other factors that may be associated with post-lung transplant survival that is also associated with the "exposure" UCTD): age, BMI

Power calculations: The 1-year survival post-lung transplant for patients with IPF is 65%, 3-year survival 50% and 5-year survival 38% based on published data[7]. Since there is no published literature regarding the post-transplant survival rate of patients with idiopathic NSIP associated with UCTD, based on our hypothesis that these patients have worse outcomes, we estimate 1-year survival to be 50%. Based on control group proportion of 0.65 and study group proportion 0.50, power calculations for the chi-square test with 80% power and $p<0.05$, we would need at least 182 patients in each group.

Statistical Analysis: Due to right censoring from shorter follow-up of more recently transplanted patients, survival data will be analyzed with Kaplan-Meier survival estimates. Cox proportional hazards model will be used to adjust for potential confounders. Secondary outcomes are both continuous variables and will be analyzed with t-test and adjusted with multivariate linear regressions.

Limitations of study: Idiopathic NSIP with UCTD may still be a relatively rare occurrence, so if we do not have enough cases for our study group, there are several potential options to help execute the study: 1) combine data from another lung transplant center cohort; 2) increase the number of controls (altering the study group/control group ratio); 3) instead of looking at

survival as the primary end point, look for a clinical marker of worse outcome, e.g. number of infections requiring hospitalization per year, as the sample size required would be smaller. Residual confounders may also be difficult to identify because idiopathic NSIP with UCTD is still a relatively newly characterized clinical entity.

References:

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