The Effect of Statin use on Fev1 in Lung Transplant Patients.

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A. Study purpose and rationale

Since the first successful lung transplantation nearly a quarter of a century ago, the procedure has gained widespread acceptance as a therapeutic option for a multitude of advanced cardiopulmonary disorders. Due largely to its relatively high prevalence, COPD is the most common indication for lung transplantation accounting for nearly 50% of all transplants[1]. Other indications include cystic fibrosis, idiopathic pulmonary fibrosis, primary pulmonary hypertension and Eisenmenger's syndrome.

The allocation of lung allografts differs from that of other solid organs in that it is based principally on length of time on waiting list without regard for severity of illness or medical urgency[2]. A ninety-day credit is awarded to patients with IPF due to their disproportionately high mortality rate on the waiting list[3]. The lung is the most fragile organ in a brain-dead donor, it is subject to damage by excessive administration of fluid, aspiration and ventilator associated pneumonia. The lung typically can tolerate less than 6 hrs of ischemia. This limits the geographic distribution of lung allografts as well as routine HLA crossmatching[4]. Donors are typically matched on the basis of major blood groups and size.

Due in part to some of the aforementioned factors, survival after lung transplant lags behind those of heart and liver transplant for which 5 yr survival is ~70-75%[5]. The five year survival after lung transplant is ~43% with median survival being 3.7 yrs[1]. It is difficult to ascertain whether lung transplantation truly increases survival over the natural history of the individual diseases without randomized trails. A disease specific comparison of patients awaiting transplantation demonstrated that transplantation likely offers a survival advantage in patients with CF and IPF; there appeared to be no clear survival advantage in patients with COPD[6].

The HMG-CoA reductase inhibitors appear to have a variety of anti-inflammatory, immunologic and cellular effects independent of its cholesterol lowering effect[7]. Mevalonate (whose synthesis is inhibited by statins) acts as an intermediate for isoprenoids which are a source of hydrophobic precursor groups that covalently bind to and activate the Ras GTPase proteins[10]. This superfamily of proteins are critical regulatory factors of signal transduction that have a myriad of complex effects on cell differentiation, prolifereation and apoptosis. Anti-inflammatory effects mediated by statins seem to be associated with its ability to block the interaction between leukocytes and endothelial surface[11]. Basement membrane degradation by lymphocytes is likely suppressed because of inhibition by matrix metalloprotease-9[12]. Functional effects of these actions could result in inhibition of cell adherence and diapedesis across the endothelium.

The efficacy of statins in solid-organ transplant is not well established. Prior reports describe improved outcomes among cardiac transplant though not among renal transplant patients[7-9]. A recent retrospective cohort study published in the Am J Respir Crit Care Med[7] suggested improvement in clinical outcomes after lung transplantation. Two hundred patients were evaluated (39 in the statin group and 161 in the non-statin group) and substantial benefits were demonstrated including a 6 yr mortality difference 54% vs 91% ($P < 0.01$). We intend to conduct a retrospective cohort study to evaluate the affect of statin use on pulmonary function in lung transplant patients.

B. Study Design and Statistical Analysis

To address the specific the aims of our study, we will conduct a retrospective cohort study of patients who have undergone lung transplantation at CPMC since 1998. We will subsequently extract the primary variables of interest (PFT) and any potential confounders including HLA type, CMV status,

ischemic time, immunosuppresive history, singe vs double LT and donor age. We will also extract markers of overall state of health such as cholesterol and albumin.

The primary outcome to be measured is the rate of change in fev1 as it relates to statin use. All patients will have had their pulmonary function tests (PFT) performed at CPMC with quantities ranging from 3-10 times a year. We will be looking at PFTs (Fev1) of patients for a 1 yr time period 3 months to 15 months post op. We will evaluate the rate of change in Fev1 between groups of patients taking a statin and those not taking statins. The rate of statin use in our transplant population is ~25%. Based on data obtained from previous studies[7] an expected difference in rate of change of predicted fev1 between statin and non-statin is 10%/yr +/-6. The unpaired student t-test will be used to analyze inter group differences if the values are parametrically distributed and the Wilcoxon-Rank Sum test should the result be nonparametrically distributed. With the alpha set at 0.05, power of 80% and an estimated 20 patients in our statin group we will be able to detect and difference of 5.5%/yr difference in the rate of change in Fev1.

We also intend on evaluating intra group differences associated with the use of statins. Patient's pulmonary function tests will be evaluated 6 months prior to and 1 year after the onset of statin use. As in the inter group analysis, we will be evaluating the rate of change over time. If the results are parametrically distributed the results will be analyzed using a paired t-test and the Wilcoxon-Rank Sum test should the result be nonparametrically distributed. Estimating a mean difference in the rate of change in fev1 of 5%/yr +/- 5% with the alpha set at 0.05, power of 80% and an estimated 20 patients in our statin group we will be able to detect a difference of 3.3%/yr in the rate of change in Fev1 associated with the use of statins.

C. Study Procedure

We will compile a list of eligible patients using the Lung Transplant Center database at Columbia-Presbyterian Medical Center. Only the investigators will have access to this list, which will contain personal identifiers. The data will be entered into an Access database, which will be privy only to study investigators.

D. Study Drugs

N/A

E. Medical Device

N/A

F. Study Questionnaires

N/A

G. Description of Subjects

The subjects to be chosen for this study must have had their transplant performed at CPMC from January 1998-January 2003.

a. Inclusion criteria

All patients who have undergone transplantation at CPMC as described above.

b. Exclusion criteria

All patients who died prior to the study period will excluded as will any patients who died as a result of graft failure during the study period (eg. secondary to CMV pneumonia, bronchiolitis obliterans). Patients who have taken statins but not for the duration of the study will be excluded from the analysis.

H. Recruitment of Subjects

The cohort will be assembled as described above.

I. Confidentiality of Study Data

We will institute strict procedures to maintain confidentiality. Personal identifiers will not appear in any presentation of the results of this study. Patient names will not be used and all of the data will be reported in aggregate. All personally identifiable information will be kept strictly confidential in a locked file cabinet and on a locked computer hard-drive. Only the investigators will have access to the data.

J. Conflict of Interest

The investigator has no financial interest

K. Location of the Study

All the analysis will be done at CPMC.

L. Potential Risks

As this is a retrospective study, the only potential list is loss of confidentiality. All of the patient information will be kept in a password secured computer.

M. Potential Benefits

The patients in the study will not benefit the patients directly but it may help in the management of future patients.

N. Alternative Therapies

N/A

O. Compensation to Subjects

There will be no compensation offered to subjects.

P. Costs to Subjects

Patients will not incur any costs as the result of this protocol.

Q. Minors as Research Subjects

There will be no minors used in this study. All patients used in this study will be >18 years of age.

R. Radiation or Radioactive Substances

N/A

S. References

1. Hosenpud JD, et al. The registry of the international society for heart and lung transplantation: the fifteenth official report-1998. J Heart Lung Transplant 1998;17:656-68
2. Hauptman PJ, et al. Procurement and allocation of solid organs for transplantation. NEJM 1997; 336:422-31
3. Hayden AM, et al. Primary diagnosis predicts prognosis of lung transplant candidates. Transplantation 1993;55:1048-50
4. Arcasoy SM, et al. Lung Transplantation. NEJM 1999;340:1081-1091
5. 1997 Annual report of the U.S. scientific registry for transplant recipients and the Organ Procurement and Transplantation Network-transplant data: 1988-1996. Richmond, Va.: United Network for Organ Sharing, 1997.
6. Hosenpud JD, et al. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. Lancet 1998;351:24-27
7. Johnson BA, et al. Statin Use Is associated with Improved Function and Survival of Lung Allografts. Am J Respir Crit Care Med 2003;167:1271-1278
8. Sahu KM, et al. Effect of lovastatin, an HMG-CoA reducatase inhibitor on acute renal allograft rejection. Clin Transpl 2001;15:173-175
9. Kobashigawa JA, et al. Effect of pravastatin on outcomes after cardiac transplantation. NEJM 1995;333:621-627
10. Khwaja A, et al. Phenylation inhibitors in renal disease. Lancet 2000;355:741-744
11. Weitz-Schmidt G., et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med 2001;7:687-692
12. Wong B, et al. Statins suppress THP-1 cell migration and secretion of matrix metalloproteinase 9 by inhibiting geranylgeranylation. J Leukoc Biol 2001;69:959-962