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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Erratic tacrolimus exposure, assessed using the standard deviation of trough blood levels, predicts chronic lung allograft dysfunction and survival

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KEYWORDS:
erratic tacrolimus levels;
lung transplant;
chronic lung allograft dysfunction;
CLAD;
death

BACKGROUND: Erratic tacrolimus blood levels are associated with liver and kidney graft failure. We hypothesized that erratic tacrolimus exposure would similarly compromise lung transplant outcomes. This study assessed the effect of tacrolimus mean and standard deviation (SD) levels on the risk of chronic lung allograft dysfunction (CLAD) and death after lung transplantation.

METHODS: We retrospectively reviewed 110 lung transplant recipients who received tacrolimus-based immunosuppression. Cox proportional hazard modeling was used to investigate the effect of tacrolimus mean and SD levels on survival and CLAD. At census, 48 patients (44%) had developed CLAD and 37 (34%) had died.

RESULTS: Tacrolimus SD was highest for the first 6 post-transplant months (median, 4.01; interquartile range [IQR], 3.04–4.98 months) before stabilizing at 2.84 μg/liter (IQR, 2.16–4.13 μg/liter) between 6 and 12 months. The SD then remained the same (median, 2.85; IQR, 2.00–3.77 μg/liter) between 12 and 24 months. A high mean tacrolimus level 6 to 12 months post-transplant independently reduced the risk of CLAD (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.63–0.86; $p < 0.001$) but not death (HR, 0.96; 95% CI, 0.83–1.12; $p = 0.65$). In contrast, a high tacrolimus SD between 6 and 12 months independently increased the risk of CLAD (HR, 1.46; 95% CI, 1.23–1.73; $p < 0.001$) and death (HR, 1.27; 95% CI, 1.08–1.51; $p = 0.005$).

CONCLUSIONS: Erratic tacrolimus levels are a risk factor for poor lung transplant outcomes. Identifying and modifying factors that contribute to this variability may significantly improve outcomes.

J Heart Lung Transplant ■■■■;■:■■■–■■■

Chronic loss of allograft function is the major cause of morbidity and mortality after transplantation, and its prevention rightly remains one of the main focuses of post-transplant care. In the lung, this process is now termed chronic lung allograft dysfunction (CLAD) and is characterized by a permanent 20% decline in forced expiratory volume in 1 second (FEV_1) over the best achieved after transplant. CLAD is associated with reduced quality of life and increased mortality after lung transplantation.[1–6] Acute rejection remains the most important risk factor.[7]

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2015.05.028

The currently available immunosuppressive agents (typically a corticosteroid, a cell-cycle inhibitor, and a calcineurin inhibitor) are generally very effective at preventing the development of acute rejection if therapeutic drug levels can be reached.[6,8–10] Of these agents, cyclosporine led to the biggest step-change in the success of solid organ transplantation, with more recent evidence supporting a slight advantage for tacrolimus over cyclosporine in lung transplantation.[11–16]

Therapeutic drug monitoring of tacrolimus trough levels is essential to achieve adequate immunosuppression while minimizing toxicity. Although the mean drug level required to prevent rejection has been well studied, little attention has been paid to the effect of erratic tacrolimus exposure, but with a satisfactory mean, in lung transplantation.[15,17–22] There are good reasons to believe that erratic exposure may be just as deleterious as sub-therapeutic tacrolimus exposure, but this possibility has been little explored.

High tacrolimus trough level variability, assessed using the standard deviation (SD), increases the risk of acute rejection early after adult lung transplant, but its affect on CLAD and survival are unknown.[23] In the liver and kidney transplant literature, an association has been found between high intrapatient tacrolimus level variability and late graft failure.[24–26] This has not been assessed in adult lung transplant recipients. We aimed to assess the effect of the mean tacrolimus trough level as well as variation in tacrolimus trough levels, assessed using SD, on the development of CLAD and survival after adult lung transplantation. We also aimed to identify factors that influence tacrolimus trough level variability.

Methods

This study was approved by the Prince Charles Hospital Human Research and Ethics Committee. A retrospective review was performed of the medical records of patients who underwent lung transplantation at our center between 1996 and 2013 and had received tacrolimus for at least the first year after transplant. Patients who were prescribed cyclosporine after the first 6 months were excluded. Almost all patients (97%) were prescribed twice-daily tacrolimus. Our center has been using basiliximab routinely for induction therapy and tacrolimus as the preferred calcineurin inhibitor since April 2011. Before this, cyclosporine was the preferred calcineurin inhibitor, with tacrolimus reserved for patients experiencing refractory acute rejection while receiving cyclosporine, or in women, excessive hair growth. Azithromycin has been used for prevention of bronchiolitis obliterans syndrome since April 2009. The practice of vaccination, anti-biotic, and anti-fungal use did not alter. No changes in the prescription of corticosteroids or cell-cycle inhibitors or in the timing of surveillance biopsies (Weeks 3, 6, and 12 and Months 6 and 12) were made during the study period.

There were no changes in tacrolimus management during the study period. The oral tacrolimus dose was given (commencing dose of 0.15 mg/kg/day; target trough level, 5–15 μg/liter) in 2 divided doses, 1 hour before or 2 hours after food. Target trough levels were 5 to 15 μg/liter (10–15 μg/liter for 0–6 months, followed by 5–10 μg/liter from 6 months). Individual target ranges varied, taking into account history of rejection, infection, and other adverse effects, but not pre-transplant diagnosis. Tacrolimus dose adjustments for cystic fibrosis (CF) patients were made as for the non-CF cohort. Oral pancreatic enzyme replacement was provided to CF patients with pancreatic insufficiency.

Tacrolimus monitoring was performed thrice weekly for the first 2 weeks after transplant, then twice weekly for 4 weeks, weekly for 1 month, and then fortnightly for 1 month. For patients with stable levels, further blood draws were performed monthly until 6 months and then every 3 months thereafter. Levels were checked 3 to 4 days after tacrolimus dose adjustments and twice weekly for inpatients.

Collected data included patient demographics, date of transplant, time after transplant or date of death, disease indication for transplant, type of transplant, and tacrolimus blood trough levels. Acute rejection burden was assessed by summing the A grades in the first 12 months. CLAD was defined as a 20% fall from the best post-transplant FEV_1 according to the evolving International Society of Heart and Lung Transplant guidelines.[27] Respiratory function tests were performed at 2 weeks after transplant and then twice weekly for 4 weeks, weekly for 1 month, fortnightly for 1 month, and then every 3 months thereafter. Patients performed daily home spirometry and were instructed to present to the clinic if they had a reduction of $\geq$ 10%.

Tacrolimus trough levels were measured as part of routine post-transplant care in inpatients and outpatients by 2 pathology providers using liquid chromatography-tandem mass spectrometry or immunoassay (Abbott Architect, EMIT 2000), with good correlation shown between the methods.[28] The mean and SD tacrolimus trough level was determined for each recipient in each of the post-transplant epochs of 0 to 6 months, 6 to 12 months, and 12 to 24 months.

Data were analyzed using Stata 11 software (StataCorp LP). A p-value of < 0.05 was considered statistically significant. The results are presented as median and interquartile range (IQR). The time from transplant to CLAD or death was modeled using Cox proportional hazard regression. Potential predictors included demographic factors (sex, age at transplant, donor type [circulatory or brain death]), transplant type, indication for transplant), clinical factors (use of induction therapy, sum of A grades, primary graft dysfunction grades), and tacrolimus mean and SD trough levels during the time periods as stated. The final model was obtained by forwards and backwards selection, retaining covariates where inclusion or exclusion changed the coefficients of other predictors by more than 10% or where predictors were statistically significant at $\alpha = 0.05$. Simple and multivariate linear regressions were performed with tacrolimus SD as the dependent variable. Simple linear regression analysis was initially used to evaluate the relationship between variables, and SD and those variables in which p was < 0.1 were then subjected to multiple linear regression analysis.

Results

Cohort Characteristics

The study included 110 patients (56% women), who were a median age of 41.3 (IQR, 27.6–51.6) years. Table 1 reports the baseline characteristics. Most patients (87%) had bilateral transplants, and the indications for transplant were CF in 47%, chronic obstructive pulmonary disease in 26%, pulmonary fibrosis in 8%, and other in 21%. Median follow up was 60 (IQR, 30.6–95.7) months. At census, 37 patients (34%) had died and 48 (44%) had developed CLAD.