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The impact of pre-transplant allosensitization on outcomes after lung transplantation

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allosensitization;
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BACKGROUND: Allosensitization can be a significant barrier to transplantation for some patients, and previous studies suggested that pre-transplant allosensitization was associated with worse outcomes after lung transplantation. However, human leukocyte antigen (HLA) antibody testing has evolved significantly over the past 10 years, and current assays are highly sensitive and specific.

METHODS: We examined the impact of pre-transplant allosensitization on post-transplant outcomes in the era of solid-phase multiplex HLA antibody detection assays in this retrospective, single-center study of 304 adult transplant recipients between January 1, 2006, and December 31, 2012. We accepted donor organs for allosensitized patients if a virtual crossmatch was compatible with all previously identified antibodies.

RESULTS: In univariate and multivariate Cox proportional hazards models, pre-transplant allosensitization, the calculated panel reactive antibody, and the number of pre-transplant HLA antibodies were not associated with the development of acute cellular rejection, lymphocytic bronchiolitis, donor-specific HLA antibodies, chronic lung allograft dysfunction, or graft failure.

CONCLUSIONS: Pre-transplant allosensitization does not adversely affect outcomes after lung transplantation when the potentially reactive HLAs are avoided in the donor by a virtual crossmatch with the recipient.

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Lung transplantation is the ultimate treatment option for patients with end-stage lung disease. However, long-term survival after transplantation is disappointing, and the leading cause of death is chronic lung allograft dysfunction (CLAD).[1] Multiple studies have identified the development of donor-specific human leukocyte antigen (HLA) antibodies (DSA) after transplantation as an important risk factor for the development of CLAD, lymphocytic bronchiolitis (LB), acute cellular rejection (ACR), antibody-mediated rejection, and death.[2–10] However, the impact of pre-transplant HLA antibodies, or allosensitization, on post-transplant outcomes is less clear, and previous studies have generated conflicting results.

An early study using the complement-dependent cytotoxicity (CDC) assay concluded that pre-transplant allosensitization was uncommon, and a modestly elevated panel

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reactive antibody (PRA) was not a risk factor for CLAD, ACR, or death.[11] In contrast, another study showed that patients who had a PRA > 10% required prolonged mechanical ventilation immediately after transplantation, were more likely to develop CLAD, and had a trend to worse survival.[12] A subsequent multicenter study using the CDC assay showed that recipients with a PRA >25% were more likely to have a positive crossmatch and had a higher risk of death in the early post-transplant period.[13]

The increased morbidity and mortality associated with allosensitization after transplantation suggests that recipients may have had pre-existing DSA that were not detected by the CDC assay, ultimately resulting in HLA-incompatible transplants. An analysis of the United Network for Organ Sharing registry found that a PRA >25% was an independent risk factor for death after transplantation between 1987 and 1997, but not between 1998 and 2005.[14] The authors proposed that advancements in HLA antibody detection methods improved donor selection and minimized the effects of allosensitization on post-transplant outcomes in the more recent era. Antibody analysis using solid-phase multiplex methods has allowed precise identification of antibody specificity, and potential donors with unacceptable HLA that would be expected to result in a positive direct crossmatch can be avoided. Use of this virtual crossmatch can expand the donor pool and improve waitlist outcomes.[15]

The impact of pre-transplant allosensitization on long-term outcomes after transplantation in the era of solid-phase multiplex HLA antibody detection assays and virtual crossmatching has not been evaluated. We hypothesized that virtual crossmatching based on sensitive and specific HLA antibody detection assays would ameliorate the impact of pre-transplant allosensitization on post-transplant outcomes.

Methods

Study design

We conducted a retrospective cohort study including all patients listed for lung transplantation at our program between January 1, 2006, and December 31, 2011. During this period, 368 patients were listed for transplantation; 3 subsequently underwent transplant at another institution and were excluded. Of the remaining 365 patients, 304 underwent transplant at our center before December 31, 2012, and comprise this cohort. The remaining 61 patients died while on the waitlist, were removed from the waitlist before transplantation, or were still waiting on December 31, 2012. We conducted a separate study examining the impact of pre-transplant allosensitization on waitlist outcomes; those results are not presented here.[16] Our institutional review board approved this study as part of our lung transplant registry protocol.

Clinical management

At listing, we screened all patients for pre-formed HLA antibodies using the LABScreen Single Antigen assay (One Lambda, Inc., Canoga Park CA). Thereafter, we repeated antibody testing every 3 months in patients while on the waitlist and 2–4 weeks after a potentially allosensitizing event. The histocompatibility laboratory at our center defines HLA antibody positivity as reactivity with a mean fluorescence intensity (MFI) ≥2,000. We used this cutoff for antibody detection before and after transplantation and computed the calculated panel reactive antibody (CPRA) using the United Network for Organ Sharing calculator.[17] We defined allosensitization as any HLA antibodies, either historical or current, with an MFI ≥2,000, and we accepted donor lungs if a virtual crossmatch was compatible with all previously identified antibodies. At the time of transplant, we performed a direct CDC crossmatch in all patients.

We treated recipients with anti-thymocyte globulin or basiliximab for induction immunosuppression and used tacrolimus, azathioprine or mycophenolate mofetil, and prednisone for maintenance immunosuppression. We performed surveillance bronchoscopies at 1, 2, 3, 6, and 12 months after transplantation; when clinically indicated; and 3–6 weeks after an episode of ACR. We screened recipients for DSA using the LABScreen Single Antigen assay at 1, 2, 3, 6, and 12 months after transplantation and when clinically indicated. We examined bronchoscopy and nasopharyngeal swab samples for community-acquired respiratory viruses (CARV) using a fluorescent-antibody assay and culture until March 1, 2013. After March 1, 2013, we used a multiplex viral polymerase chain reaction assay and defined any positive result as a CARV infection. We measured spirometry weekly for the first 12 weeks, monthly for the remainder of the first year, then every 1–3 months thereafter. We diagnosed CLAD according to the International Society for Heart and Lung Transplantation (ISHLT) guidelines.[18,19]

Statistical analysis

We compared categorical variables using the chi-square test and continuous variables using the Student's *t*-test for normally distributed data and the Wilcoxon's rank sum test for skewed data. We defined graft failure as death or re-transplantation. We examined freedom from ACR, LB, CLAD, DSA, and graft failure using the Kaplan-Meier method and compared groups using the log-rank test. We constructed univariate and multivariate Cox proportional hazards models to evaluate the impact of different variables on the development of DSA, CLAD, and graft failure. In all models, we evaluated DSA, ACR, LB, CLAD, and CARV infections as time-dependent variables to avoid assigning risk before their development. In addition, we included only 1 time-dependent variable in each multivariate model to avoid risk over-inflation; this resulted in 4 multivariate models. We conducted statistical analysis using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp.).

Results

Baseline characteristics and histocompatibility

Follow-up was complete through December 31, 2013, and the study included 974 patient-years of follow-up with a mean follow-up of 3.2 ± 1.9 years. Among the 304 recipients, 108 (35.5%) were allosensitized before transplantation, and 196 (64.5%) were not allosensitized (Table 1). Overall, there was no significant difference in baseline characteristics between recipients who were allosensitized and recipients who were not allosensitized (Table 1). Among the 108 allosensitized recipients,

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