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Human leukocyte antigen–DR13 and DR15 are associated with short-term lung transplant outcomes

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ABSTRACT

Background: Lung transplantation outcomes are among the least favorable, with most recipients eventually developing bronchiolitis obliterans syndrome (BOS) and subsequent graft failure. The presence of human leukocyte antigen (HLA)-DR has been implicated in the pathogenesis of BOS and may play a role in these poor outcomes.
Methods: Lung transplant donor and recipient data were retrospectively gathered from the United Network for Organ Sharing database from January 2006 to June 2013. Donor and recipient characteristics, proportion of recipients treated for first year rejection, and 5-y rates of survival and freedom from BOS were determined according to HLA-DR1, -DR7, -DR13, and -DR15 status in both donor and recipient. Each HLA-DR allele was stratified by donor–recipient pair positivity status.
Results: A total of 7402 lung transplant recipients met the inclusion and exclusion criteria. There were significant but small differences in donor and recipient characteristics for each HLA-DR group. The recipients in the $D^{-}R^{+}$ pairing for HLA-DR13 and those in the $D^{+}R^{-}$ pairing for HLA-DR15 had significantly higher rates of receiving treatment for rejection within the first year after transplant ($P = 0.024$ and $P = 0.001$, respectively). There were no differences in 5-y survival or freedom from BOS for any of the four HLA-DR alleles studied.
Conclusions: There are higher rates of patients treated for rejection within the first year who are either negative for the HLA-DR15 allele but received a donor-positive lung or positive

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for the HLA-DR13 allele but received a donor-negative lung for that allele. However, these differences do not appear to affect long-term outcomes.

Introduction

Survival after lung transplantation is among the least favorable compared with that of other available solid organ transplant procedures nowadays.[1,2] Bronchiolitis obliterans syndrome (BOS) is a pathologic change in the lung that is characterized by a fibro-obliterative process of the small airways,[3] occurring months to years after transplantation.[4] By 10 y after transplantation, 74% of recipients develop BOS.[4] The development of BOS is a frequent precursor to eventual graft failure and mortality.[4] Therefore, identifying methods to reduce the likelihood of this highly morbid complication to increase survival is an important goal.

In the past decade or so, there has been considerable research in elucidating the pathogenesis behind BOS. An autoimmune mechanism has been studied, where a high degree of recipient autoreactivity to type V collagen [col(V)] is associated with increased incidence and severity of BOS.[3] In that study, human leukocyte antigen (HLA)-DR mismatch was also found to be significantly associated with the risk of developing severe BOS.[3] A follow-up article by Keller *et al.*[5] looked at the relationship between specific HLA-DR alleles and col(V) positivity in both donors and recipients. They found that an HLA-DR15$^+$ donor may in fact increase the risk of the recipient's development of col(V) autoimmunity and severe BOS.[5] The article also noted that unpublished findings of a single-center analysis of 278 lung transplant patients showed that recipients with an HLA-DR15$^+$ donor lung trended toward developing severe BOS.[5] They also found that col(V) positive recipients were more likely to have the HLA-DR1 allele but less likely to have the HLA-DR13 allele than controls.[5] In addition, there are numerous other reports of HLA mismatches, including HLA-DR–specific mismatches, being associated with decreased survival and increased incidence of BOS.[6-9] However, to our understanding, there is currently no published large-scale study that compares the survival and incidence of BOS with respect to donor and recipient HLA-DR positivity in the aforementioned alleles. Establishing a significant relationship between HLA-DR positivity and poor outcomes, as well as delineating whether it is important in either donor or recipient or both, would aid in choosing the most favorable combination of HLA-DR allele status in the initial organ donation matching process.

Methods

Subjects

Lung transplant recipient data were gathered from the United Network for Organ Sharing database during the period January 2006 to June 2013. Inclusion criteria included those who were older than 18 y, had an isolated lung transplant, did not have a prior lung transplant, and had classification of HLA-DR status. Those with missing HLA-DR classification data were excluded. Recipient and corresponding donor characteristics were obtained. The Indiana University Institutional Review Board classified this study as exempt.

Outcomes

Donor and recipient characteristics were compared according to HLA allele positivity as follows: donor-positive, recipient-positive (D^+R^+); donor-positive, recipient-negative (D^+R^-); donor-negative, recipient-positive (D^-R^+); and donor-negative, recipient-negative (D^-R^-). Having at least one positive allele was considered to be positive. HLA allele positivity was determined for HLA-DR1, -DR7, -DR13, and -DR15.

For each HLA allele examined, recipient outcomes were also compared according to the four donor and recipient pairs (D^+R^+, D^+R^-, D^-R^+, and D^-R^-). These outcomes included the proportion treated for rejection in the first year, survival rates at 5 y, and freedom from BOS at 5 y. In this analysis, "BOS" was defined as at least grade 1 BOS.

Statistical methods

For each of the HLA-DR groups, the donor–recipient pairs were compared for characteristics of both donor and recipients, using the analysis of variance for continuous variables (expressed as the mean and standard deviation) or chi-square test for categorical variables (expressed as the count and percentage). The rates of treatment for rejection in the first year were compared by donor–recipient pairs for each of the HLA-DR groups, along with corresponding chi-square tests to evaluate the significant difference. Multivariate logistic model was used to adjust for factors that were found to be significantly different between the donor and recipient pair groups. Kaplan–Meier survival curves were constructed for 5-y survival and 5-y freedom from BOS of recipients, stratified by the four donor–recipient pairs. Association of the donor–recipient pairs with survival rate and freedom from BOS was evaluated using a univariate log-rank test. Cox proportional hazards models were run separately for each survival curve, with adjusted significant factors based on the multivariate logistic model described previously. A P-value of <0.05 is considered statistically significant. All analyses were performed using Statistical Analysis Software (SAS) version 9.3 (SAS Institute Inc, Cary, NC).

Results

Donor and recipient characteristics

A total of 7402 lung transplant recipients met the inclusion and exclusion criteria. Tables 1-4 list the characteristics of