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Influence of human leukocyte antigen mismatching on bronchiolitis obliterans syndrome in lung transplantation

Don Hayes Jr., MD, MS,[a,b,c,f] Sylvester M. Black, MD, PhD,[c] Joseph D. Tobias, MD,[d,g] Benjamin T. Kopp, MD,[a,f] Stephen E. Kirkby, MD,[a,b,f] Heidi M. Mansour, PhD,[e] and Bryan A. Whitson, MD, PhD[c]

From the Departments of [a]Pediatrics; [b]Internal Medicine; [c]Surgery; [d]Anesthesiology, The Ohio State University College of Medicine, Columbus, Ohio; [e]Skaggs Pharmaceutical Sciences Center, University of Arizona–Tucson College of Pharmacy, Tucson, Arizona; [f]Section of Pulmonary Medicine; and the [g]Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio.

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survival

BACKGROUND: Varying results have been reported in the investigation of human leukocyte antigen (HLA) mismatching and bronchiolitis obliterans syndrome (BOS) after lung transplantation (LTx).

METHODS: The UNOS database was queried for the period 1997 to 2013 to examine HLA mismatching and its association with BOS in LTx.

RESULTS: Of 16,959 first-time adult LTx recipients, 16,854 were included in the univariate Cox analysis and Kaplan–Meier survival function evaluation, and 14,578 were included in multivariate Cox models. Multivariate Cox analysis showed that the number of total HLA mismatches was significantly associated with greater hazard of BOS (HR = 1.060; 95% CI 1.013 to 1.108; $p = 0.011$), as was the presence of 2 HLA-A mismatches, when compared with 0 or 1 mismatch at that locus (HR = 1.128; 95% CI 1.026 to 1.240; $p = 0.012$). These results were confirmed using competing-risks regression models that adjusted for death before BOS diagnosis. Multivariate Cox models identified no significant association with BOS hazard for HLA-B (HR = 1.014; 95% CI 0.914 to 1.126; $p = 0.785$) or HLA-DR (HR = 1.085; 95% CI 0.987 to 1.193; $p = 0.090$) mismatches. Higher body mass index was associated with increased risk for BOS, whereas older age was protective against BOS. Induction with alemtuzumab (HR = 0.343; 95% CI 0.252 to 0.467; $p < 0.001$) or basiliximab (HR = 0.862; 95% CI 0.758 to 0.980; $p = 0.023$) and longer ischemic time (HR = 0.909; 95% CI 0.877 to 0.942; $p < 0.001$) were associated with lower hazard of BOS.

CONCLUSIONS: Total HLA mismatches are associated with increased risk for BOS, specifically at the A locus. Induction with alemtuzumab or basiliximab reduced the risk, whereas greater ischemic time appears to also be protective.

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Chronic lung allograft dysfunction, particularly bronchiolitis obliterans syndrome (BOS), which is the clinical counterpart of obliterative bronchiolitis (OB), has emerged as the major obstacle to long-term survival after lung transplantation (LTx).[1] Within 5 years of LTx, 40.3% of

Reprint requests: Don Hayes, Jr., MD, MS, Section of Pulmonary Medicine, The Ohio State University, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205. Telephone: +614-722-3425. Fax: +614-722-3426.

E-mail address: hayes.705@osu.edu

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first-time adult recipients develop BOS.[1] Although the pathogenesis of BOS has not been completely characterized, multiple immunologic factors have been described as contributing to its development, including innate immunity response, cellular/humoral alloimmunity and cellular/humoral autoimmunity.[2]

T-cell receptors recognize the allogeneic major histocompatibility complex (MHC), also termed human leukocyte antigen (HLA), on the donor cells via a direct pathway and peptide fragments of allogeneic MHC presented by recipient MHC molecules through an indirect pathway.[3,4] Although the role of humoral alloimmunity in BOS is not as well recognized, anti-HLA antibodies after LTx are associated with increased risk of BOS and decreased survival.[5–14] Several studies have demonstrated HLA mismatching between donor and recipient enhancing the risk for BOS and reducing graft survival, but there is a lack of consistency in the reported involvement of specific loci.[5–14]

With uncertain findings regarding HLA mismatching as a precursor for the development of BOS after LTx, we sought to assess the effect of total HLA mismatching as well as mismatches specifically at the A, B and DR loci using a database available in the United States. We hypothesized that HLA mismatching contributes to the development of BOS. With no previous research investigating the effect of induction immunosuppression on these HLA mismatching effects, we included contemporary induction agents in the adjusted models to determine their impact on the hazard risk (HR) of BOS associated with HLA mismatching, while also evaluating the role of graft ischemic time.

Methods

Data collection

We retrospectively evaluated data from patients who were registered in the Organ Procurement and Transplant Network (OPTN) Standard Transplant Analysis and Research (STAR) thoracic database,[15] administered by United Network for Organ Sharing (UNOS). Our study was approved by institutional review board of The Ohio State University Wexner Medical Center with a waiver of the need for individual consent (IRB # 2012H0306). The UNOS/OPTN thoracic database was queried for all adult ($\geq$18 years of age) patients between January 1997 and September 2013 who were first-time recipients of single or bilateral LTx from cadaveric donors. Patients with a history of re-transplantation (n = 33), patients induced with muromonab-CD3 (n = 170) and patients with incomplete data on HLA mismatch (n = 2,839) were excluded, leading to a sample size of 16,959. Patients who received muromonab-CD3 were excluded, as this agent is no longer available for clinical use.

Statistical methods

All analyses were performed using STATA/MP, version 13.1 (StataCorp LP, College Station, TX). Descriptive statistics for continuous variables are presented as mean and standard deviation, and descriptive statistics for categorical variables are presented as proportions. BOS onset was assessed at follow-ups scheduled for 6 months after LTx and each subsequent anniversary of LTx. BOS diagnosis was reported dichotomously (yes/no) until 2004, at which point differentiation between Grade 0p, Grade 1, Grade 2 and Grade 3 BOS was introduced. For consistency across years, BOS follow-up data were dichotomized as 1 = BOS diagnosed at follow-up (any grade, if applicable) vs 0 = BOS not yet diagnosed at any follow-up. Missing data on BOS onset were primarily due to attrition before the first follow-up. There were 2,458 patients (14.49%) with no BOS data who exited before the 6-month mark; 662 (3.90%) with no BOS data exiting after 6 months but before the next scheduled follow-up at the first anniversary of LTx; and 319 (1.88%) with no BOS data exiting 1 year or later after LTx. In the main analysis, cases of missing data on BOS were coded as not having been diagnosed with BOS at any follow-up. Re-analysis of the data set while excluding all 3,439 cases missing BOS data did not alter the findings reported (results available upon request).

The main covariates of interest were total HLA mismatch level (continuous variable, with a range of 0 to 6) and mismatch at the A, B or DR locus, respectively (each dichotomized as 2 vs 0 or 1). Survival analysis was performed on time from LTx to the date of follow-up at which BOS was diagnosed, up to a maximum follow-up duration of 5 years (range of time to BOS diagnosis: 82 to 1,825 days). There were 105 cases with unknown or zero time spent at risk, and these were excluded from our analysis. Univariate survival analysis relating each covariate to the diagnosis of BOS after LTx was performed using Kaplan–Meier function curves and a log-rank test of differences in survival functions, and Cox proportional hazards models. Multivariate survival analysis was performed using Cox proportional hazards models to test the relationship between each main covariate and the hazard of developing BOS, controlling for recipient characteristics, donor characteristics and transplant characteristics. In Kaplan–Meier and Cox proportional hazards analyses of time to BOS onset, both death and loss to follow-up were treated as censoring events. To represent BOS onset and mortality before BOS onset as competing risks, multivariate competing-risks regression models were fitted using the Fine and Gray method.[16] The exclusion of cases missing data on control variables reduced the sample size of the multivariate models to 14,578 cases.

Cytomegalovirus (CMV) mismatching between recipient and donor may be associated with BOS and may coincide with HLA mismatching,[5] but data on CMV mismatching are substantially incomplete in the UNOS database. Therefore, we performed a supplementary multivariate Cox proportional hazards analysis in a sub-sample of 8,863 patients, adding CMV mismatching as a covariate, where donor-negative (D^-) recipient-negative (R^-) was the reference group, and comparison groups included D^-R^+, D^+D^- and D^+R^+.

Results

Study population

Table 1 summarizes patients' demographics and characteristics of the sample used for analysis. Of 16,959 first-time, adult LTx recipients, only 18 (0.11%) had 0 mismatch whereas 637 (3.76%) had 2 or fewer mismatches. Due to the rarity of patients with no HLA mismatches, 0 and 1 mismatches were compared with 2 mismatches at each specific locus. There were 8,529 patients (50.29%) with 2 mismatches at the A locus, 11,926 patients (70.32%) with 2 mismatches at the B locus and 9,167 patients (54.05%) with 2 mismatches at the DR locus.