Effect of sensitization in US heart transplant recipients bridged with a ventricular assist device: Update in a modern cohort

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Objective: Preformed anti-human leukocyte antigen antibodies have been associated with prolonged wait times and increased mortality in orthotopic heart transplantation. We used United Network for Organ Sharing data to examine panel reactive antibody titers in patients bridged to transplant with left ventricular assist devices.

Methods: This was a retrospective review of the United Network for Organ Sharing dataset for all patients bridged to orthotopic heart transplantation with a HeartMate II or HeartMate XVE (Thoratec Corp, Pleasanton, Calif) from January 2004 to December 2009. Patients were primarily stratified by device type and secondarily grouped for comparisons by high (>25%) versus low (0%) panel reactive antibody activity (class I and II). Outcomes included survival (30-day and 1-year), treated rejection in the year after orthotopic heart transplantation, and primary graft dysfunction. Cox proportional hazards regression examined 30-day and 1-year survival.

Results: A total of 871 patients (56.1%) received the HeartMate II device, and 673 patients (43.9%) received the HeartMate XVE device. Patients with high panel reactive antibody had longer duration on the wait list (205 days [interquartile range, 81–344] vs 124 days [interquartile range, 51–270], $P = .01$). High panel reactive antibody class II was more common in patients with the HeartMate XVE device (51/547 [9.3%] vs 42/777 [5.4%], $P < .001$). When the entire cohort was examined together, there was no 30-day or 1-year survival difference based on panel reactive antibody activity. Device type did not affect post-orthotopic heart transplantation survival, and panel reactive antibody activity was not associated with worse mortality in Cox regression. Although panel reactive antibody activity did not affect rejection in the year after orthotopic heart transplantation for either device type, high panel reactive antibody class II was associated with higher rates of primary graft dysfunction for both devices ($P < .05$).

Conclusions: This is the largest modern study to examine the impact of detailed panel reactive antibody information in patients bridged to transplant. High panel reactive antibody levels do not affect drug-treated rejection episodes in the first year post-orthotopic heart transplantation; however, there is an associated higher rate of primary graft dysfunction, regardless of device type. Highly sensitized patients bridged to transplant experience excellent survival outcomes after orthotopic heart transplantation. (J Thorac Cardiovasc Surg 2011;142:1236-45)

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Past studies have considered left ventricular assist device (LVAD) implantation to be a sensitizing event, resulting in elevations of anti-human leukocyte antibody (HLA) levels.[1-4] Panel reactive antibody (PRA) levels are frequently used to quantify this sensitization. The Food and Drug Administration approval of LVAD therapy as a bridge to heart transplantation has led to increasing numbers of patients awaiting orthotopic heart transplantation (OHT) with LVADs in place.[5] Although some studies have cited increased mortality in highly sensitized patients bridged to transplant who undergo transplantation, particularly with older-generation pulsatile flow devices,[6-8] there are other studies that document equivalent post-OHT survival in sensitized and nonsensitized patients.[9] Also, patients with high PRA levels undergoing conventional OHT are known to experience longer wait-list time and worse 1-year survival.[10] However, many of these studies are limited by small sample size and continually evolving laboratory techniques. It is unclear whether the observed outcome differences persist on a national scale among all US patients bridged to transplant in

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Abbreviations and Acronyms

HLA = human leukocyte antibody
HMII = HeartMate II
LVAD = left ventricular assist device
OHT = orthotopic heart transplantation
PGD = primary graft dysfunction
PRA = panel reactive antibody
UNOS = United Network for Organ Sharing
XVE = HeartMate XVE

the modern era of immunomodulatory therapy. Therefore, we used United Network for Organ Sharing (UNOS) data to examine outcomes among highly sensitized patients bridged to OHT.

MATERIALS AND METHODS

Data Source

The UNOS Standard Transplant Analysis and Research database represents an open cohort of prospectively collected donor specific and follow-up data from October 1987 to December 2009. The dataset used comprises all US patients undergoing thoracic organ transplantation, with follow-up to June 2010. No patient or center identifiers were included, and the study was granted institutional review board exemption.

Study Design

This study was a retrospective cohort design, including adult (>17 years) patients undergoing primary OHT as a bridge to transplant with the HeartMate II (HMII) or HeartMate XVE (XVE) device (Thoratec Corp, Pleasanton, Calif) from January 2004 to December 2009. PRA major histocompatibility class is not distinguished before 2004 in the UNOS database, and thus the study began in 2004. Exclusion criteria included incomplete ventricular assist device data, heart-lung transplantation, prior OHT, and missing PRA information. The cohort was stratified according to device type (HMII vs XVE).

Panel Reactive Antibody

PRA levels closest to the time of transplant were used in all patients. Interventions to desensitize patients and timing of ventricular assist device implant are not available in the UNOS database. Thus, PRA levels at listing and peak PRA levels were not evaluated. Highly sensitized patients were defined as having a PRA greater than 25%, and nonsensitized patients were defined as having a PRA of 0%. Strata of PRA activity were defined according to the following groups: 0%, greater than 0% to 10%, greater than 10% to 25%, and greater than 25%. Class I and II PRA levels were first examined separately. Because sensitization has been reported in the pediatric OHT literature as an elevated PRA level regardless of class, we also defined a composite PRA score as the highest PRA level in either class.[11] Comparisons between high (>25%) and low (0%) PRA activity were performed for both device types. Additional PRA information not contained within the Standard Transplant Analysis and Research file was provided by UNOS. Specifically, 4 categories of PRA assay methods were identified: (1) cytotoxicity assays, (2) enzyme-linked immunosorbent assays, (3) flow cytometry assays, and (4) other.

Variables Examined and Outcome Measures

The dataset contains more than 400 preoperative, intraoperative, and postoperative variables. Variables examined included primary diagnosis; demographics (age, sex, race, education, and insurance); pre-OHT mechanical ventilation or intensive care unit admission; comorbidities (diabetes mellitus, percent ideal body weight, serum creatinine levels, and hypertension); and transplant variables (ischemic time, HLA mismatch, transplant year, and wait-list time). In addition, hemodynamic measurements (mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac index) were examined. Donor variables examined were age, race, sex, cytomegalovirus status, diabetes, and cigarette use.

The primary end point was 1-year mortality. Secondary outcomes examined were short term mortality (30-day), rejection requiring treatment within the first year after OHT, primary graft dysfunction (PGD), and drug-treated infection. In the UNOS database, PGD is self-reported and defined by each individual center.

Statistical Analysis

We compared baseline characteristics between the high versus low PRA groups (class I and II separately) by the Student *t* test (continuous variables) and chi-square test (categoric variables). Survivals of 30 days, 90 days, and 1 year were estimated using the Kaplan–Meier method, because these time intervals have adequate follow-up in this dataset. The Mantel–Cox log-rank test was used to compare survival estimates according to PRA activity. The entire cohort was analyzed according to the Kaplan–Meier method. Separate Kaplan–Meier analysis was performed for XVE and HMII to assess the impact of device type.

A multivariable Cox proportional hazards regression model estimated risk of death with censoring for death, loss to follow-up, and administrative reasons (end of study period). To construct the multivariable model, independent covariates with potential for confounding were first tested in a univariate fashion. In addition to variables associated with mortality on exploratory analysis ($P < .2$), those with biological plausibility and previously recognized risk factors were incorporated in a forward and backward stepwise fashion into the multivariable model. The likelihood ratio test and Akaike's information criterion in a nested model approach were used to identify which covariates increased the explanatory power of the model. This method favors more parsimonious models. Because the multivariable model was developed with case-wise deletion, all covariates with greater than 15% missing data were not included. The final model for 1-year mortality incorporated the following covariates: recipient age, heart failure cause, race, recipient serum creatinine, recipient serum bilirubin, pre-OHT infection requiring intravenous antibiotics, preoperative mechanical ventilation, allograft ischemic time, center volume, device type (XVE vs HMII), and PRA activity. Although the model was explored with PRA activity as a categoric variable or incorporating strata of PRA activity, the Akaike's information criterion favored PRA as a categoric variable (>25%). Visual inspection of complementary log-log plots and testing of Schoenfeld residuals for each variable confirmed that the assumption of proportional hazards had not been violated.

Means are presented with standard deviations, and medians are presented with their interquartile range. Hazard ratios are displayed with 95% confidence intervals. Statistical testing was performed using STATA software (version 11; StataCorp LP, College Station, Tex).

RESULTS

Cohort Statistics

From 2004 to 2009, 1672 patients underwent OHT as a bridge to transplant with an XVE or HMII device in the UNOS database. In regard to device type, 938 patients (56.1%) received an HMII and 734 patients (43.9%) received an XVE. PRA information was missing in 128 patients (7%); thus, the final cohort consisted of 1544 patients (n = 673, XVE; n = 871, HMII). The mean age of the cohort was 52 ± 12 years, and 84.8% were male

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