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Early donor-specific antibodies in lung transplantation: Risk factors and impact on survival

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BACKGROUND: The impact of early donor-specific anti-HLA antibodies (DSA) on patient and graft survival after lung transplantation remains controversial. In this study we analyzed risk factors for DSA that developed before initial hospital discharge after lung transplantation (early DSA) and compared mid-term outcomes in patients with or without DSA.

METHODS: Between January 2009 and August 2013, 546 patients underwent lung transplantation at our institution. One hundred (18%) patients developed early DSA (Group A) and 446 (82%) patients (Group B) did not. Patient records were retrospectively reviewed.

RESULTS: Retransplantation (odds ratio [OR] = 2.7, 95% confidence interval [CI] 1.1 to 6.5, $p = 0.03$), pre-operative HLA antibodies (OR = 2.1, 95% CI 1.2 to 3.4, $p = 0.003$) and primary graft dysfunction (PGD) score Grade 2 or 3 at 48 hours (OR = 2.6, 95% CI 1.5 to 4.6, $p = 0.001$) were associated with early DSA development. Overall, 1- and 3-year survival in Group A and B patients was 79 ± 4% vs 88 ± 2% and 57 ± 8% vs 74 ± 3%, respectively ($p = 0.019$). Eleven Group A (11%) and 32 Group B (7%) patients died before hospital discharge ($p = 0.34$). Among patients surviving beyond discharge, 1- and 3-year survival in Group A and B patients was 89 ± 4% vs 95 ± 1% and 65 ± 8% vs 80 ± 3% in Group A and B patients, respectively ($p = 0.04$). Multivariate analysis identified early anti-HLA Class II DSA (OR = 1.9, 95% CI 1.0 to 3.4, $p = 0.04$) as an independent risk factor for post-discharge mortality but not for in-hospital mortality.

CONCLUSIONS: Pre-operative HLA antibodies, retransplantation or post-operative PGD increase the risk of developing early DSA, which were independently associated with an increased risk for mortality. J Heart Lung Transplant 2014;33:1255–1263

Lung transplantation is an established therapy for end-stage lung diseases.[1] However, long-term graft survival remains constrained by bronchiolitis obliterans syndrome (BOS).[2,3] Multiple immunologic and non-immunologic factors have been associated with the development of BOS.[4–8]

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There has been recent interest on the impact of anti-human leukocyte antigen (anti-HLA) antibody development and humoral rejection.[9–16] Donor-specific antibodies (DSA) appear to influence long-term graft and patient survival.[17–19] In the absence of accepted diagnostic criteria[20] or treatment for humoral rejection, and given that the majority of existing data have been derived from small, retrospective studies, reaching conclusions on management and prognosis remains difficult. In addition, controversy about the importance of DSA prevails, given reported observations of patients demonstrating DSA over longer periods without developing any clinical features of rejection.[21]

Few studies have investigated early post-operative DSA development.[14,17–19] In this study we aimed to identify risk factors for early DSA development and to compare outcomes in patients with or without DSA at a high-volume lung transplantation center.

Methods

Patients

Between January 2009 and August 2013, 546 patients underwent lung transplantation at our institution. All patients were included in the analysis. One hundred patients (Group A; 18%) showed a positive crossmatch or developed DSA before initial hospital discharge after lung transplantation, whereas 446 did not (Group B). Only patients who developed early DSA during their initial hospital stay after lung transplantation were included in Group A. Data were collected by reviewing patient records. Follow-up ended on November 1, 2013 and was 100% complete. Mean follow-up was 23 ± 16 months (range 1 to 58 months).

During lung transplantation surgery, cardiopulmonary bypass (CPB) was employed for hemodynamic support until April 2010. Since then, extracorporeal membrane oxygenation (ECMO) has been used instead, due to its versatility and better post-operative patient outcome.[22]

Immediately after arrival at the intensive care unit, all patients received a single dose of anti-cytomegalovirus (CMV)-enriched hyperimmunoglobulins. No induction therapy was administered. Post-transplant immunosuppression comprised a triple therapy (calcineurin inhibitor, mycophenolate mofetil and prednisolone). During the first year after transplantation, trough levels of 8 to 12 μg/liter and 180 to 220 μg/liter were targeted for tacrolimus or cyclosporine, respectively.

The hospital ethics committee, which approved the study, waived the need for patient consent for inclusion in the study.

Variables

The CMV risk profile, the need for post-operative or secondary ECMO support, BOS and primary graft dysfunction (PGD) have been defined elsewhere.[2,22,23]

Pre-operative recipient demographics include the variable "autoimmune disease" referring to patients with pathologies such as connective tissue disease that could confer a higher immunologic risk. The intra-operative variable, "lung volume reduction," refers to a surgical resection of a lobe or a segment of the transplanted lungs due to a size mismatch between donor and recipient. Because not all assumed and treated episodes of acute rejection were biopsied and confirmed histologically, two distinct entities were defined for analysis. First, all steroid-responsive deteriorations in lung function after exclusion of other causes were defined as "pulsed steroid therapies." Second, biopsy-diagnosed acute rejections were defined according to International Society for Heart and Lung Transplantation (ISHLT) guidelines.[24] At our institution, surveillance transbronchial biopsies are performed at 1, 3 and 6 months and at 1 year after transplantation and upon indication.

DSA detection and therapy

Recipients were screened for anti-HLA antibodies immediately before lung transplantation, on Day 14, and again before hospital discharge, using complement-dependent cytotoxicity (CDC; Bio-Rad Medical Diagnostics GmbH, Dreieich, Germany) and Luminex (LIFECODES; Immucore Transplant Diagnostics, Inc., Stamford, CT) assays.[25,26] A threshold of 1,000 mean fluorescence intensity (MFI) was used to define anti-HLA antibody positivity. The highest MFI value was considered in patients who showed DSA against more than one antigen.

Treatment of early DSA was usually performed irrespective of presence of graft dysfunction. Upon DSA detection before April 2013, patients were treated with three to five sessions of plasma exchange and a single dose of rituximab (375 mg/m^2), whenever possible. Since May 2013, this protocol has been superseded by treatment with IgM-enriched intravenous immunoglobulins (IVIg; Pentaglobin, Biotest Pharma GmbH, Dreieich, Germany) with an initial 1-g/kg body weight loading dose and a single dose of rituximab (375 mg/m^2) followed by additional courses of 0.5 g/kg IVIg every 4 weeks until DSA clearance. After discharge, DSA in Group A were assessed at regular outpatient visits only if clinically indicated. However, DSA were controlled in all surviving Group A patients between July 2013 and November 2013. Group B patients were only tested in the event of subsequent deterioration in graft function during follow-up.

Data analysis

Data collection and analysis were performed retrospectively using SPSS version 21.0 (IBM, Armonk, NY). Primary end-points were DSA development, mortality, pulsed steroid therapy and biopsy-confirmed acute rejection. BOS development was monitored. Categorical and continuous variables were summarized as percentage and mean ± standard deviation (SD), respectively. To avoid data skewness, median values with interquartile range (IQR) were reported for intubation times, intensive care unit and hospital stays and time to DSA development. The independent-samples Student's *t*-test or the non-parametric Mann–Whitney *U*-test and the chi-square test or Fisher's exact test were used for group comparisons of continuous and categorical variables, respectively. These tests were also used to identify univariate associations with the primary end-points. Two-tailed $p \leq 0.05$ was considered significant. Survival estimates along with freedom from pulsed steroid therapy and biopsy-confirmed acute rejection were calculated using the Kaplan–Meier product-limit method.

Multivariate analysis, using a forward stepwise logistic regression model, was performed to identify independent risk factors for DSA development and in-hospital mortality. Model calibration was evaluated using the Hosmer–Lemeshow (H-L) goodness-of-fit test. A Cox regression analysis was performed to identify independent risk factors for mortality conditioned to hospital discharge. Results are reported as odds ratios (ORs) with a 95% confidence interval (CI) and corresponding *p*-value.