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Preemptive treatment with therapeutic plasma exchange and rituximab for early donor-specific antibodies after lung transplantation

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OBJECTIVE: De novo donor-specific anti-human leukocyte antigen antibodies develop in a high proportion of lung transplant recipients early after lung transplantation. We recently showed that de novo donor-specific antibodies (DSA) occurrence is associated with significantly increased mortality. Here, we studied the efficacy of a preemptive treatment protocol.

METHODS: A retrospective observational study was conducted on all lung transplantations at Hanover Medical School between January 2009 and May 2013.

RESULTS: Among the 500 transplant recipients, early DSA developed in 86 (17%). Of these, 56 patients (65%; Group A) received therapeutic plasma exchange, and 30 patients (35%; Group B) did not. Among Group A patients, 51 also received rituximab. Between groups, there was no statistically significant difference in mortality, incidence of pulsed steroid therapies, rejections diagnosed by biopsy specimen, incidence of bronchitis obliterans syndrome (BOS), or infections requiring hospitalization at 1 year and 3 years. Also, there were no statistically significant differences after matching 21 Group A with 21 Group B patients through propensity score analysis. Significantly more Group A patients (65%) than Group B patients (34%) cleared DSA at hospital discharge ($p = 0.01$). At the last control after transplantation (median, 14 months; interquartile range, 5–24 months), 11 Group A (22%) and 9 Group B patients (33%) still showed DSA ($p = 0.28$).

CONCLUSIONS: Preemptive treatment with therapeutic plasma exchange and rituximab led to improved elimination of DSA early after lung transplantation ($p = 0.01$). However, spontaneous elimination in untreated Group B patients also occurred frequently. This treatment protocol was not associated with significantly improved outcome.

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Development of de novo donor-specific human leukocyte antigen (HLA) antibodies after lung transplantation has been identified as a risk factor for patient and graft survival.[1–9] We recently demonstrated that patients developing early

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donor-specific antigen (DSA) after lung transplantation had a worse survival compared with patients without DSA and that early anti-HLA II DSAs were an independent risk factor for death.[10] However, the efficacy of treatment for DSA is controversial.

In keeping with other solid-organ transplantations,[11–15] intravenous immune globulin (IVIG) or therapeutic plasma exchange (tPE) with 1 dose of rituximab have been used to clear DSA in lung transplantation.[16–18] Treatment with IVIG and a single dose of rituximab was demonstrated to clear DSA effectively in a subgroup of patients and to confer a survival advantage in DSA patients in whom the antibodies cleared, but the absence of a control group and randomization may have biased that study.[16] So far, no single-case series using tPE and rituximab in lung transplantation have been reported, but treatment protocols that included tPE and rituximab in kidney transplantation effectively cleared DSA without increasing morbidity.[11,12]

At our institution, we instituted preemptive treatment for de novo DSA with tPE and rituximab from 2009 until 2013, irrespective of graft dysfunction. This study compared early and midterm follow-up between DSA patients who did and did not undergo treatment.

Methods

The hospital Ethical Committee approved this study and waived the need for patient consenting to the study.

Patients

A retrospective study was performed in a single university center, where 500 patients underwent lung transplantation between January 2009 and May 2013. All patients who developed de novo DSA early during the initial hospital stay after lung transplantation formed the study population. Patients who developed DSA at follow-up after hospital discharge were not included.

Data were collected by retrospectively reviewing patient records and outpatient visits. Follow-up ended on November 1, 2013. Follow-up regarding survival was 100% complete.

Cell saver was used in all patients intraoperatively, and no autologous blood replacement was used. All patients underwent treatment with a single dose of human immunoglobulins against cytomegalovirus immediately upon arrival at the intensive care unit. No induction therapy was administered. Immunosuppressive therapy was based on a triple therapy with a calcineurin inhibitor, mycophenolate mofetil, and prednisolone.

Variables

The cytomegalovirus risk profile, the need for post-operative or secondary extracorporeal membrane oxygenation support, bronchiolitis obliterans syndrome (BOS), and primary graft dysfunction (PGD) have been defined elsewhere.[19–21]

The pre-operative variable "autoimmune disease" refers to patients with pathologies such as connective tissue diseases, Crohn disease, and graft-versus-host disease after bone marrow transplantation that might confer a higher immunologic risk. Immunologic mechanisms leading to autoimmunity are comparable to the mechanisms leading to development of anti-HLA antibodies or autoantibodies against collagen V and tubulin after lung transplantation.[22–24]

Because a histologically confirmed biopsy specimen was not available for all assumed and treated episodes of acute rejection, 2 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 the International Society for Heart and Lung Transplantation (ISHLT) guidelines.[25] At our institution, protocol surveillance transbronchial biopsies are performed at 1, 3, and 6 months, and 1 year after transplantation and upon indication. In this study, incidence of acute humoral rejection at follow-up was not reported. Owing to unspecific pathologic diagnostic criteria for acute humoral rejection,[26] the lung pathologists at our institution never made the diagnosis.

Infection occurring at follow-up after the initial hospital stay for transplantation was defined as a bacterial, fungal, or viral infection that needed hospitalization and treatment.

DSA detection and tPE

Recipients were screened for anti-HLA antibodies immediately before lung transplantation, on day 14, and before hospital discharge using complement-dependent cytotoxicity assay (Bio-Rad Medical Diagnostics GmbH, Dreieich, Germany) and a LIFECODES Luminex assay (Immucor Transplant Diagnostics Inc, Stamford, CT).[27,28] However, additional controls were performed in some patients, for example. if rejection was suspected or if samples were accidentally sent for analysis. A low threshold of 1,000 mean fluorescence index (MFI) was used to detect early-onset DSA. The highest MFI value was considered if more than 1 HLA specificity was detected.

As soon as DSAs were detected, a cycle of 3 or 5 sessions of tPE was begun, whenever possible, irrespective of graft dysfunction. A control sample was performed before treatment was initiated. A 5-session cycle was usually performed in patients with a positive crossmatch or with higher MFI values without a specific upper cutoff defined. MFI values ranged above 13,000 in these patients. A 3-session cycle was applied to the remaining patients. A single dose of rituximab (375 mg/m^2) was administered at the end of the first cycle of tPE. A second cycle of tPE was performed if DSA recurred or had not been completely cleared after the first cycle.

The exchange volume specified by the protocol was 1.2 to 1.5 times the calculated plasma volume using the Nadler/Allen equation. An albumin solution was used as replacement fluid, with the exception of patients with a high risk of bleeding or serum fibrinogen levels below 120 mg/dl. Treatment was performed using a double-lumen dialysis catheter inserted in the internal jugular or femoral vein using heparin or citrate anti-coagulation. All patients received prophylactic antibiotic treatment during tPE. In those patients who survived to discharge, DSAs were again assessed after a median of 14 months (interquartile range [IQR], 5–24 months).

Statistics

Data were collected retrospectively. SPSS 21.0 (IBM Corp, Armonk, NY) and the propensity score matching extension from the SPSS Extension Bundle were used to perform data analysis. Primary end points were death, incidence of pulsed steroid therapies, specimen-confirmed acute rejections, BOS, and development of infections requiring hospitalization. Continuous variables are summarized as median values (IQR) and categoric variables as percentages. The non-parametric Mann-Whitney *U* test and the