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Research Paper

Donor-specific antibodies require preactivated immune system to harm renal transplant

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ABSTRACT

Background: It is an unresolved issue why some kidney transplant recipients with pretransplant donor-specific HLA antibodies (DSA) show a high transplant failure rate, whereas in other patients DSA do not harm the graft. We investigated whether help from preactivated T-cells might be necessary for DSA to exert a deleterious effect.

Methods: The impact of pretransplant DSA and immune activation marker soluble CD30 (sCD30) on 3-year graft survival was analyzed in 385 presensitized kidney transplant recipients.

Findings: A deleterious influence of pretransplant DSA on graft survival was evident only in patients who were positive for the immune activation marker sCD30. In the absence of sCD30 positivity, 3-year graft survival was virtually identical in patients with or without DSA (83.1 ± 3.9% and 84.3 ± 2.8%, $P = 0.81$). A strikingly lower 3-year graft survival rate of 62.1 ± 6.4% was observed in patients who were both sCD30 and DSA positive (HR 2.92, $P < 0.001$). Even in the presence of strong DSA with ≥5000 MFI, the 3-year graft survival rate was high if the recipients were sCD30 negative.

Interpretation: Pretransplant DSA have a significantly deleterious impact on graft survival only in the presence of high pretransplant levels of the activation marker sCD30.

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1. Introduction

Kidney transplants involving recipients who possess lymphocytotoxic antibodies against mismatched HLA antigens of the donor are at high risk of antibody-mediated rejection. In today's clinical practice such transplants are generally avoided (Tait et al., 2013). A complement-dependent cytotoxicity (CDC) crossmatch that detects donor-directed antibodies in the patient's sera was introduced in the 1970's and, supplemented by the flow cytometry version, allows the exclusion of unfavorable recipient donor combinations (Patel and Terasaki, 1969). The CDC technique has the drawback of not being highly sensitive and has been criticized for not detecting all clinically relevant antibodies. During recent years, more sensitive solid-phase assays based on ELISA, flow cytometry and Luminex® platforms were introduced for detection and specification of donor-specific HLA antibodies (DSA), and the pretransplant inclusion of HLA antibody specificities in the recipient's waiting list profile for allowing exclusion of 'unacceptable HLA antigen mismatches' in the 'virtual crossmatch' has become routine practice (Tait et al., 2013). Of modern antibody assays, the Luminex® single antigen bead (SAB) technique has, despite the drawback that it occasionally gives false positive results due to the presence of denatured HLA on the bead surface (Cai et al., 2009), the highest sensitivity and resolution and is therefore used widely.

Contradictory results were obtained with respect to whether all pretransplant DSA detected by the sensitive SAB technique are deleterious (van den Berg-Loonen et al., 2008; Eng et al., 2008). In a retrospective study, we found that the incidence of pretransplant DSA was not higher in kidney recipients with graft loss than in recipients with functioning grafts if the antibodies were reactive exclusively in the SAB assay but not in the less sensitive CDC or ELISA assays (Susal et al., 2011). While the antibodies often seemed to act as mediators of allograft destruction, we and others noticed that, in some recipients, antibodies persisted but did no harm to the graft or disappeared (Susal et al., 2015; Knight et al., 2013).

The complement (C)-activating capacity of DSA, indirectly assessed by classical pathway component C1q binding, was proposed as a discriminator between deleterious and non-harmful antibodies (Chen et al., 2011; Loupy et al., 2013). However, in today's practice most patients with pretransplant C1q-binding DSA are excluded from transplantation because these antibodies, if sufficiently strong, react positively in the CDC crossmatch. In retrospective testing, pretransplant C1q-binding DSA were therefore rare in patients who received a transplant after routine crossmatching (Otten et al., 2012). Even if detected pretransplant, they often disappeared after transplantation without inflicting harm (Schaefer et al., 2016). In a small cohort of six patients with graft loss due to antibody-mediated rejection, we obtained preliminary evidence that the deleterious effect of pretransplant DSA might be related to *T*-cell help originating from a preactivated immune system (Schaefer et al., 2016). T-cell support is required for the switch of B cells to plasma cells that produce antibodies with high affinity for mismatched donor HLA. Previous data showed that increased levels of the immune system activation marker soluble CD30 (sCD30) are associated with an increased risk of graft loss (Susal et al., 2002; Heinemann et al., 2007; Saini et al., 2008).

Because of our previous failure to find an association of graft failure with pretransplant DSA that exclusively reacted in the exquisitely sensitive SAB assay (Susal et al., 2011), we focused in the present study on pretransplant sera containing CDC- or ELISA-reactive antibodies, selected without regard to donor-specificity. Antibodies detected with these assays of lower sensitivity have been found in the past to correlate with kidney graft outcome (Schonemann et al., 1998; Susal and Opelz, 2002). In patients possessing such antibodies, we analyzed whether pretransplant HLA antibodies with donor specificity, as identified in the highly sensitive SAB assay, might require a preactivated immune system, as indicated by high serum sCD30 at the time of transplantation, as a prerequisite for unfolding a deleterious action.

2. Methods

2.1. Patients

Adult (≥18 years old) recipients of deceased donor kidney transplants who were transplanted 1996–2011 were studied retrospectively. Patients with multi-organ transplants were excluded. We selected all 385 patients from the Collaborative Transplant Study (CTS) combined serum and DNA study (www.ctstransplant.org) whose last pretransplant serum was reported by the participating centers to be positive in the CDC panel reactivity assay (PRA) or who tested positive in the CTS serum study for ELISA-reactive HLA antibodies (AbScreen, Biorad, Dreieich, Germany). These patients were termed "presensitized" and their frozen-stored serum and DNA specimen were used for additional testing. Based on previous findings, an optical density (OD) of ≥0.300 in ELISA and >0% reactivity in the CDC-PRA assay were used as cut-offs for positivity (Susal and Opelz, 2002). Thirteen transplant centers participated both in the serum and the DNA study, and transplants from these centers were selected for the current project. The availability of DNA on recipients and their respective donors allowed for the retrospective typing of HLA A, B, C, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, and DPB1 antigens, and thereby the precise definition of DSA. Patient consent and ethics committee approval was obtained and the investigations were performed in accordance with the Declaration of Helsinki. Demographic characteristics of the patients are shown in Table 1. Only 11 (3%) of the patients had an incomplete 3 year follow-up. Characteristics of patients subdivided into further subgroups according to sCD30 positivity or negativity are shown in Supplementary Table S1.

2.2. Measurements

The sera of the 385 presensitized patients were tested in the Heidelberg laboratory for serum sCD30 content using the ELISA kit of eBioscience (San Diego, USA) and for HLA antibodies using the LABScreen kits of One Lambda (Canoga Park, CA) which utilize single HLA antigen-coated beads and enable the identification of IgG alloantibody specificities against HLA A, B, C, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, and DPB1. No clinical cut-off for these assays is recommended by the provider companies. The receiver operating characteristic curve analysis, in which 3-year graft as well as death-censored graft survival was analyzed at five different cut-offs (70, 80, 90, 100, 110 ng/ml), indicated 80 ng/ml as the most suitable cut-off for sCD30 testing. Based on experience from previous studies (Susal et al., 2011), a mean fluorescence intensity (MFI) of ≥1000, was considered positive for HLA antibody reactivity. For high resolution typing of HLA A, B, C, DRB1, DQA1, and DQB1 antigens at the allele level, CTS PCR-SSP Tray and CTS-Sequence Kits (Heidelberg, Germany), and for HLA DRB3, DRB4, DRB5 and DPB1 typing Olerup SSP kits (Saltsjöbaden, Sweden) were used. All DSA positive sera were analyzed for the presence of C1q-binding antibodies using the C1qScreenTM kit of One Lambda and applying a cut-off of 300 MFI (Chen et al., 2011).

2.3. Statistical analysis

Graft as well as death-censored graft survival rates were computed according to the Kaplan-Meier method and are expressed as % ± standard error. Log-rank test, Fisher's exact test, Mann-Whitney U test and multivariable Cox regression were used for statistical analysis. In multivariable analysis, geographic region, year and number of transplant, recipient and donor gender and age, original disease causing end stage renal failure, pretransplant clinical evaluation of the patient, HLA-A + B + DR mismatches, pretransplant time on dialysis, and intention-to-treat immunosuppressive therapy (antibody induction, calcineurin inhibitors, anti-proliferatives) were considered as confounders. Patients negative in sCD30 and DSA testing served as reference group for the calculation of hazard ratios. *P* values below 0.05 were considered

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