Oral Presentations

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De Novo Donor Specific Antibodies: The Impact on Graft Survival and Rejection in Renal Transplantation

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The presence of *de novo* donor specific antibodies (dnDSA), has been associated with poor transplant outcomes, including high incidence of antibody-mediated rejection, graft dysfunction, and inferior graft survival. Moreover, dnDSA can appear before graft loss, suggesting that dnDSA may represent a mechanism of repetitive injury and a potential prognostic biomarker (1-3). The development of dnDSAs after kidney transplant were reported in 13-30% of previously non-sensitized patients (4-6). DnDSA are predominantly directed to donor human leukocyte antigen (HLA) class II mismatches and usually occur during the first year of kidney transplant, but they can appear any time, even several years later (7). This study was based on the identification of donor-specific anti-HLA antibodies, their complex characteristics including antibody classes, HLA specificity, strength, immunoglobulin G subclass, and complement binding capacity in long-term post-transplant follow-up of patients, as well as their impact on graft survival.

This retrospective study included forty-one pediatric patients aged <18 years, who received first renal transplants at the University Children's Hospital, Belgrade, Serbia, between January 2008 and December 2018. All patients were non-sensitized and had been transplanted from ABO compatible donor with negative complement-dependent cytotoxicity (CDC) crossmatch. Nineteen patients underwent transplantation from a living donor and 22 from a deceased donor. Serum samples were collected at 0, 3, 6, 12 months and yearly thereafter, or at the time of biopsy when clinically indicated (graft dysfunction or suspicion of rejection). Sera were screened for HLA-specific antibodies using CDC (One Lmbda LCT 60 and in house panel) and solid-phase Luminex antibody-detection beads (Luminex, LMX, Immucor). Selected HLA-specific antibody-positive samples were analyzed using Luminex single-antigen class I and class II antibody-detection beads (lifecodes LSA1, LSA2). Specificities with mean fluorescence intensity values (MFI) >2000 were considered positive. If donor-specific antibodies were absent pretransplant, as determined by solid phase assays and became detectable post-transplant they were classified as dnDSA. All patients continue to be prospectively tested for dnDSA according to the serum collection schedule outlined above to detect new dnDSA or to assess the persistence of existing dnDSA.

During a mean follow-up time of 6.1±4.5 years, 20/41 (48%) patients developed dnDSA. Although the group of living donor kidney transplant correlated with 0-3 HLA mismatches (MM) ($p<0.01$), no statistically significant difference was proven in the presence of dnDSA in relation to the type of donor, living or deceased ($p=0.176$). By CDC method positive result for HLA antibody class I was obtained in five patients. In two cases, DSAs were confirmed, while in three others, detected antibodies were non-DSA.

By Luminex method, dnDSA class I were detected in two patients ($p<0.0001$), 12 patients had dnDSA class II only ($p<0.0001$) and both class I and II observed in 6 patients. The majority of dnDSAs were class II antibodies and HLA-DQ were among the most frequent specificity, with a statistically higher prevalence ($p<0.0001$).

Seven patients rejected the graft and were back on hemodialysis. In two cases, rejection occurred in the group of living donor recipients, in 5 cases it was in the group of deceased donor recipients. Time from the first detection of dnDSA to the graft failure was 2.7-3.9 years. Of the patients with dnDSA, all graft losses occurred in patients with MFI in the moderate, strong or very strong range with none occurring in those with weak DSA.

The 5-year graft survival was better in the group of living donor recipients. However, over a ten-year period, the log rank test did not show a significant difference in survival length between the groups (Figure 1).

The 10-year graft survival for patients with dnDSA was lower than that of the no dnDSA group (52% vs. 95%, $p<0.05$) (Figure 2). Patients with HLA-DQ DSA had lower 10-year graft survival compared to the group of patients without HLA-DQ DSA (41.3% vs. 91%, $p<0.05$) (Figure 3). The 10 - year graft survival was significantly worse when DSA were combined with non-DSA compared with DSA alone, non-DSA alone or without DSA ($p<0.05$) (Figure 4).

This study showed correlation of graft survival in relation to the type of transplantation, DSA, class of antibodies, strenghts and specificities. Patients with DSA and antibody-mediated rejection (ABMR) had lower graft survival than those without DSA. The proportion of dnDSA was high, with the majority against HLA-DQ. The detection of dnDSA prompted early diagnosis and treatment of ABMR. Long-term transplant outcomes may benefit from routine DSA monitoring. The challenge is to develop a cost-effective DSA monitoring algorithm. However, currently, there is no standard or consensus follow-up protocol for dnDSA after transplantation.

References

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