Clinical and Public Policy Implications of Pre-Formed DSA and Transplant Outcomes

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According to data from the Organ Procurement and Transplantation Network, as of May 6, 2019, approximately 95,000 candidates are awaiting kidney transplantation in the United States alone. Of these, approximately 12% have a prior failed kidney transplant and nearly 30% have a calculated panel reactive antibody percentage (cPRA) of 20% or more. Because cPRA indicates the likelihood of a patient having preformed donor specific antibody (DSA) directed against an HLA antigen of potential donors, the level of cPRA is inversely associated with the probability of receiving an HLA-compatible kidney allograft. Prior to changes made to the kidney allocation system (KAS) in the United States, highly HLA-sensitized candidates were rarely transplanted (1). Although HLA-sensitized candidates have now enjoyed increased access to kidney transplantation coinciding with allocation policy changes implemented in the United States in late 2014, kidney transplantation remains elusive for the most highly sensitized candidates (2).

In the new Kidney Allocation System (KAS) era, controversy exists as to whether increased accessibility to deceased donor kidney transplantation might obviate the need to proceed with HLA-incompatible kidney transplantation. It remains unclear which patients would benefit from earlier transplantation with an HLA-incompatible donor versus remaining on dialysis in search of better compatibility with a different donor. Factors to consider include patient preference, the relative harm of increasing dialysis time, the likelihood of finding a compatible donor, costs and complications associated with incompatible transplantation, and long-term patient and graft outcomes.

In this issue of the CJASN, Ziemann et al. (3) report outcomes following both living and deceased donor kidney transplantation performed in the presence of preformed DSA. This was a large, multicenter retrospective cohort study involving 4132 patients across 18 German transplant centers. Of these, the vast majority had no DSA at transplant (92% of living donor and 91% of deceased donor recipients), whereas relatively few did (106 living donor and 261 deceased donor recipients total). Among patients with DSA included in the study, more than half were classified as having weak binding DSA with a mean fluorescence intensity (MFI) <3000 and would not be predicted to have a positive flow crossmatch.

The salient finding of the study was that the presence of preformed DSA was associated with higher all-cause graft loss. The observation was consistent regardless of whether DSA was weak-binding (MFI<3000) or stronger binding (MFI≥3000) and was evident in both living and deceased donor recipients. The lower graft survival could not be attributed solely to higher rates of death among patients with preformed DSA; death-censored graft survival was also found to be lower among patients with preformed DSA compared with those without.

Although these findings are not particularly surprising, one must be careful about drawing conclusions regarding the impact of preformed DSA on post-transplant outcomes from a retrospective study, which can only identify association but not prove causality. One would presume that because preformed DSA is a mediator of antibody-mediated rejection, the observation of lower all-cause graft survival resulted from an excess of immunologic graft failures among those with preformed DSA. However, graft survival was not different between recipients with weak binding DSA (MFI<3000), which are generally predicted to be associated with a negative crossmatch, and those with stronger binding DSA (MFI≥3000). Furthermore, the percentage of recipients in this study who experienced antibody-mediated rejection within the first 6 months after transplant was similar among recipients with weak binding DSA compared with recipients without DSA and was only observed to be higher among recipients with stronger binding DSA. This suggests that nonimmune mechanisms may have contributed to the observation of lower graft survival among recipients with preformed DSA in this study, which is plausible considering that HLA-sensitized recipients are often medically complex, with comorbidities incurred over years of dialysis time. In this study, data on comorbid conditions were not reported and multivariable adjustment for these factors was not performed. Therefore, the relative impact of comorbidities on the observed graft outcomes is unclear.

Second, inferences are limited due to the practice of not performing flow cytometry crossmatches in this study. Prior data from a large multicenter study

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involving 22 transplant centers in the United States indicated that increasing degrees of HLA-incompatibility, ranging from presence of DSA alone with a negative crossmatch to a positive flow cytometry crossmatch to a positive cytotoxic crossmatch, were associated with progressively higher risks of post-transplantation graft loss and death (4). Graft survival was similar among patients with a negative crossmatch regardless of the presence of DSA and was only lower among recipients with either a positive flow cytometry or cytotoxic crossmatch, highlighting the superiority of physical crossmatching for risk stratification over virtual crossmatching using DSA and MFI alone. At Cedars-Sinai, we do not proceed with kidney transplantation if the flow cytometry crossmatch exceeds 250 median channel shift and we avoid transplants with a positive cytotoxic crossmatch. Although practices vary by transplant center in the United States, most centers would caution against proceeding with transplantation across a strongly positive flow crossmatch. In the current study, it is not known to what extent that the reported graft outcomes would have been attenuated if strongly positive flow crossmatches were identified and avoided.

Additionally, the study does not adequately address whether routine use of desensitization would have mitigated graft survival differences between those with DSA and those without. Our group, along with others, has reported that graft survival was not different among desensitized kidney transplant recipients compared with compatible kidney recipients (5,6). Desensitization with intravenous Ig and rituximab attenuates post-transplant antibody rebound and has been associated with a lower incidence of antibody-mediated rejection and transplant glomerulopathy (7).

Although it is reasonable to conclude from this study that preformed DSA should be avoided, this is not always possible or practical, considering that bypassing an available donor leads to an increase in dialysis time. Data indicates that HLA-incompatible live donor kidney transplantation is associated with a higher survival rate than remaining on the waiting list for a deceased donor transplant (8). Therefore, it is reasonable to recommend that candidates who have an HLA-incompatible living donor should proceed with incompatible transplantation rather than wait for a deceased donor kidney transplant. Such candidates may be offered the option of participating in a paired kidney exchange program. However, donors for broadly sensitized candidates may be difficult to exchange, particularly for sensitized candidates with blood type O, and incompatible transplantation may still be necessary. Attempts by other investigators have combined desensitization with paired exchange in efforts to increase transplant rates. Although some benefits have been seen, there remains little benefit for the most highly-HLA sensitized patients (9).

There is currently limited data on the survival benefit of HLA-incompatible deceased donor kidney transplantation compared with dialysis. Our group evaluated the efficacy of desensitization with intravenous Ig and rituximab given to highly-sensitized waitlisted candidates on time to transplant and found that desensitization was associated with a higher rate of transplantation and lower mortality compared with similarly sensitized candidates maintained on the United Network for Organ Sharing (UNOS) waitlist (10). This analysis was performed prior to recent allocation policy changes implemented with the new KAS, and similar analyses have not been performed in the post-KAS era. Efforts to delineate which patients should be recommended for an HLA-incompatible deceased donor kidney transplant are hampered by incomplete data on crossmatch results from the Organ Procurement and Transplantation Network/UNOS database. In the absence of clear data on how the KAS has affected the number of HLA-incompatible transplants, it is difficult to formulate recommendations on which candidates would fare better by proceeding with HLA-incompatible transplantation versus waiting for a more compatible donor. Multiple studies have observed lower long-term hazards of death for deceased donor kidney transplant recipients compared with waiting on dialysis. Although prior studies have not specifically addressed the survival benefit of HLA-incompatible deceased donor transplantation, it is not unreasonable to proceed with an HLA-incompatible deceased donor offer provided that the transplant center is experienced with incompatible transplantation.

The study by Ziemann et al. (3) adds to the growing body of literature about outcomes associated with HLA-incompatible transplantation; however, more data on how outcomes associated with HLA-incompatible transplantation compare with dialysis is necessary. There remains a critical need for the development of prognostic models and decision-making algorithms to help transplant centers inform recipients on whether to proceed with an HLA-incompatible transplant or wait for a more compatible offer. There is compelling data that indicates that HLA-incompatible live donor kidney transplantation has a survival benefit over dialysis; however, similar analyses need to be performed for HLA-incompatible deceased donor kidney transplantation.

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