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Original Article

Establishment of calculated panel reactive antibody and its potential benefits in improving the kidney allocation strategy in Taiwan

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Background/Purpose: Renal transplant candidates who are highly sensitized to human leukocyte antigens (HLAs) tend to wait longer to find a matched donor and have poor outcomes. Most organ-sharing programs prioritize highly sensitized patients in the allocation scoring system. The HLA sensitization status is traditionally evaluated by the panel-reactive antibody (PRA) assay. However, this assay is method dependent and does not consider the ethnic differences in HLA frequencies. A calculated PRA (cPRA), based on a population's HLA frequency and patients' unacceptable antigens (UAs), correctly estimates the percentage of donors suitable for candidates. The Taiwan Organ Registry and Sharing Center does not prioritize sensitized patients. We propose that the incorporation of the cPRA and UAs into the renal allocation program will improve the local kidney allocation policy.
Methods: We established a cPRA calculator using 6146 Taiwanese HLA-A, -B, -C, -DR, and -DQ phenotypes. We performed simulated allocation based on the concept of acceptable mismatch for 76 candidates with cPRA values exceeding 80%.
Results: We analyzed 138 waitlisted renal transplant candidates at our hospital, and we determined that the concordance rate of the cPRA and PRA for highly sensitized (%PRA $>$ 80%) candidates was 92.5%, which decreased to 20% for those with %PRA $<$ 80%. We matched 76 highly sensitized patients based on acceptable mismatch with the HLA phenotypes of 93 cadaver donors. Forty-six patients (61%) found at least one suitable donor.

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Conclusion: The application of the cPRA and acceptable mismatch can benefit highly sensitized patients and reduce positive lymphocyte cytotoxicity crossmatch.

Introduction

Patients with preformed antibodies against a donor's human leukocyte antigen (HLA) are more likely to experience hyperacute and antibody-mediated rejection, as well as other long-term transplant complications.[1,2] The development of new HLA antibodies after transplantation strongly predicts chronic immunological rejection.[1] The pre- and post-transplant HLA sensitization status of patients should be regularly monitored. Since the first successful kidney transplantation in Taiwan in 1968, studies and resources have been devoted to the establishment of an organ-sharing system and more efficient care of transplant patients and have achieved great success.[3–7] A notable milestone is the establishment of the Taiwan Organ Registry and Sharing Center (TORSC) in 2002 for standardizing the processes of organ donation, procurement, and transplantation. However, the current kidney allocation system (KAS) does not address the immunization status of waitlisted renal transplant candidates. The panel-reactive antibody (PRA) assay, reimbursed by the Taiwan health insurance policy, measures the relative degree of sensitization of patients. However, the results of the PRA assay vary with the sources of the antigen panels and methods, and the assay has limited use in the prediction of individual donor–recipient compatibility. The newly developed solid-phase-based assays that use solubilized HLAs, particularly the Luminex single antigen bead assay (hereafter, PRA-SA assay), have higher sensitivity and accuracy[2,8,9]; this assay can specifically identify unacceptable antigens (UAs) in patients.

The Organ Procurement and Transplantation Network (OPTN), operated by the United Network for Organ Sharing (UNOS), USA, has introduced the calculated PRA (cPRA) since December 2007 to provide a more uniform and accountable method for assessing sensitization to HLAs.[10] The cPRA is based on the HLA phenotype frequencies of each ethnic group and types of HLA antibodies present in a patient's serum. The cPRA value reflects UAs in patients, and renal transplant candidates with a higher cPRA value would have lower opportunities to find a matched donor. Therefore, the cPRA is a more reliable indicator of the HLA sensitization status than is the classical PRA. The UNOS implemented a new strategy on October 1, 2009, incorporating the cPRA into the kidney allocation policy. When a patient's cPRA level exceeds 80%, the patient will get additional scores and have a better opportunity for finding a potentially compatible donor.[10,11]

The TORSC does not include the PRA or cPRA in the organ allocation scoring system, and it only uses lymphocyte crossmatching to determine donor–recipient compatibility. Without knowledge of patients' UAs, organ refusals occur because of positive cytotoxic crossmatching results; therefore, laboratory examinations are inconclusive. Highly sensitized waitlisted patients have a disadvantageous condition. To develop a more efficient allocation system, developing a more informative method to detect patients' antibodies and establishing the cPRA calculator are necessary. Therefore, the objective of this study was to evaluate the feasibility of the incorporation of the cPRA into the organ allocation scoring system and the application of virtual crossmatching in Taiwan. We evaluated the agreement in the results of different PRA assays and established the cPRA calculator based on Taiwanese HLA phenotype frequencies. We demonstrated differences in the cPRA values by using HLA-A, -B, and -DRB1 UAs and HLA-A, -B, -C, -DRB1, and -DQB1 UAs. We also observed that virtual crossmatching based on the absence of UAs could benefit highly sensitized patients by improving their chances of finding a matched donor.

Methods

In July 2013, the PRA-SA assay for testing HLA antibodies was developed in the histocompatibility laboratory at the National Taiwan University Hospital (NTUH). A total of 138 waitlisted renal transplant candidates in the NTUH who were tested for solid-phase HLA antibodies from July 2013 to September 2016 were included in this study. The study was approved by the Research Ethics Board of the NTUH.

FlowPRA screening

We used the FlowPRA class I and II screening assay (One Lambda Inc., Canoga Park, CA, USA) to determine the sensitization status of waitlisted renal transplant candidates. This screening assay comprises a pool of 30 bead preparations, representing all common antigens as well as many rare HLA alleles.[12] FlowPRA $>$ 50% is defined as positive, as clinically suggested. Among all patients, 135 were subjected to FlowPRA screening.

PRA-SA assay

We identified HLA class I and II antibodies by performing the PRA-SA assay according to the manufacturer's instruction. The PRA-SA assay (LABScreen, One Lambda Inc.) is a solid-phase HLA antibody assay that uses up to 100 microbeads coated with purified class I or II HLA molecules of a single specificity, and it can detect class I or II HLA antibodies in human serum. The amount of anti-HLA antibody bound to a specific bead can be detected using the mean fluorescence intensity (MFI) after normalization against the background

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