Transplant Risk Assessment: It Is Not about the Panel Reactive Antibodies

Ahmed Daouda  Mahmoud Nassarb

aDepartment of Medicine, Cairo University Medical School, Cairo, Egypt; bDepartment of Medicine, Icahn School of Medicine at Mount Sinai/NYC Health+Hospitals, Queens, NY, USA

Dear Editor,

We have read with great interest the article written by Ali et al. [1] titled: “Outcomes of Interleukin-2 Receptor Antagonist Induction Therapy in Standard-Risk Renal Transplant Recipients Maintained on Tacrolimus: A Systematic Review and Meta-Analysis.” This meta-analysis included 12 RCTs and showed significant results and concluded that in standard-risk transplant patients maintained on tacrolimus and MMF, basiliximab induction therapy had no additional benefit compared to no-induction therapy. This conclusion was observed in previous retrospective studies [2, 3].

The authors used a broad definition for standard-risk transplant: panel reactive antibodies (PRAs) <50% and HLA mismatch <5. However, the PRAs in most of the studies included in the meta-analysis were <20%.

The presence of PRAs/HLA antibodies has been repeatedly associated with poor transplant outcomes [4]. There has been considerable debate as to what threshold of PRA percent should be considered “high risk”; now that specificities of HLA antibodies may be more precisely defined, it is clear that it is the specificity and not the percent PRAs per se that defines the clinical risk. With PRA testing output demonstrable as a continuous variable, the dichotomous approach of high versus low risk is clearly not biologically reflective of risk, which is also a continuum. The amount of antibody, as well as the specificities, contributes to the assessment of risk. Higher amounts of antibodies can be associated with more short-term clinical adverse outcomes (e.g., acute antibody-mediated rejection), whereas lower titers of antibodies may be associated with chronic pathologies or may take some time to develop into higher titers with a later presentation of acute pathology. Even a PRA of 5% may confer significant risk if the antibody it represents binds to donor antigens. A low titer antibody may become a high titer antibody if stimulated by the appropriate antigen from a donor organ and may explain why pretransplant low titer donor-specific antibodies are associated with subsequent posttransplant adverse outcomes [5]. Conversely, by defining precise antibody specificities, unsuitable donors can be avoided in high PRA patients. With the selection of an acceptably matched donor (one to whom no antibodies are directed), they can now expect comparable long-term outcomes nonsensitized patients [6]. Therefore, the detection of any HLA antibody must be followed by the interrogation of comprehensive specificities because it is those specificities, rather than a particular PRA
percent, that determine the risk assessment when considered along with the potential donor typing.

PRA percent is relevant but should be interpreted instead as an estimate of the fraction of potential donors to whom a patient has donor-directed antibody. Therefore, it represents the “risk” of donor specificity occurring, but not the risk of an immunologic event occurring.

Calculated PRA (cPRA) is a standardized approach to determine the likelihood that a recipient will have donor-specific antibodies by comparing the antibody specificities (determined on solid-phase assay locally) to the defined frequencies of HLA alleles in the population of interest nationally. A US cPRA calculator may be found on the OPTN website for public access.

Antibody to a donor may be detected on a solid phase assay even when a crossmatch is negative, owing to the high sensitivity of these tests. The significance of these findings in studies ranges from no clinical relevance [7] to an increase in short- and long-term outcomes [8].

The ability to predict a future immunologic event is based only upon the serum available after patient identification and referral. Therefore, it cannot measure antibodies that may have occurred in the past with historical sensitizing events that have subsequently waned. It does happen that when a serum appears to be free of antibodies, shortly after a repeated stimulus with a transplant, a memory response may still occur, and new antibodies develop much more quickly than the 4–6 weeks required for a de novo response [9]. As such, although essentially reassuring, negative antibody screening alone cannot completely exclude a potential memory response; clinical history of sensitizing events must always be considered even in an unsensitized recipient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Funding was not required.

Author Contributions

Ahmed Daoud: wrote the initial draft. Mahmoud Nassar: reviewed the manuscript.

References