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Editorial

"Match and treat," an effective strategy for transplanting highly sensitized pediatric transplant candidates?

The highly sensitized kidney transplant candidate presents an enigma for most transplant programs. Not only is it difficult to find a suitable donor, but it is also more likely that a kidney transplant will fail. The accumulation of highly sensitized patients on renal transplant waiting lists is a universal problem. Sensitized pediatric candidates have anti-HLA antibodies because of previous graft failures and blood transfusions. Several methods are now available to screen sera for antibodies against class I and class II HLA antigens. Because the ultimate goal is a successful transplant, any antibody specificity analysis should focus on the distinction between acceptable and unacceptable HLA mismatches among potential donors. This can be done by considering each HLA antigen as a configuration of epitopes that can be defined structurally by short polymorphic amino acid residue sequences with the HLAMatchmaker algorithm. The implementation of an HLAMatchmaker-based acceptable mismatch strategy has increased the allocation of suitable organs to highly sensitized patients. Unfortunately, some patients do not benefit from this approach because their HLA profiles have uncommon antigens and/or their sera react with almost every non-self antigen. This problem is compounded for pediatric candidates who need a suitably sized kidney from a compatible donor.

Another approach to transplanting highly sensitized patients is to remove or reduce the level of donor-specific antibodies prior to transplantation using exchange plasmapheresis, intravenous immunoglobulin (IVIG), or a combination of these procedures. The goal of these procedures is to convert the crossmatch of an HLA-mismatched donor from positive to negative, so a transplant can be performed. Although these protocols have significant success rates, there are many cases of insufficient reduction of antibody levels and humoral rejection of a subsequent transplant. Furthermore, these procedures are expensive and resource intensive.

The question remains: "Do we match or treat the highly sensitized patient?" An obvious answer would be to consider first the acceptable mismatch strategy. If this reveals an extremely low likelihood of finding a suitable donor, then proceed to antibody reduction treatment.

The report by Valentini et al. on "IVIG, HLA Allele Typing and HLAMatchmaker Facilitate Successful Transplantation in Highly Sensitized Pediatric Renal Allograft Recipients" in this issue of *Pediatric Transplantation* suggests an alternative answer namely "Match and Treat." Adjunct to the IVIG treatment protocol, the investigators used HLAMatchmaker-based criteria for defining HLA mismatch acceptability of potential donors. These criteria consider a minimalization of the number of mismatched epitopes and the avoidance of high-risk immunogenic epitopes. Such acceptable mismatches can be expected to lower the risk of antibody-mediated rejection thereby improving transplant outcome.

This approach was used for two highly sensitized pediatric patients who have been successfully retransplanted with a deceased donor kidney. Both experienced no rejection episodes and are doing well more than one year after transplantation.

These two cases suggest the utility of this acceptable mismatch protocol to select donors for highly sensitized patients after desensitization. Nevertheless, a larger and preferably multi-institutional study is needed to validate this approach, to fully define the criteria for mismatch acceptability and how to use them in respect to the likelihood of finding suitable donors.

The Valentini et al. report shows that HLA typings were done at the allele level rather than the serologically defined antigens used in most organ allocation systems. High-resolution allele typing permits a much more precise determination of mismatch acceptability and this is especially important for highly sensitized patients including those in racial minority groups. All HLA polymorphisms that produce immunogenic epitopes should be considered. They include the class I alleles of HLA-A, B and C and class II alleles of DRB1, DRB3, DRB4 and DRB5, DQA1 and DQB1 and, probably DPB1 and DPA1 as well, because all of them have epitopes that can induce specific antibodies in transplant recipients. It may seem that the inclusion of all these loci would render a matching strategy too complicated, but it offers the advantage of a more complete assessment of the HLA epitope repertoire.

The matching approach used by Valentini et al. considered the relative immunogenicity of epitopes. Immunodominant epitopes are high-risk mismatches and low-immunogenicity epitopes might be considered permissible mismatches. Epitope immunogenicity can be estimated from frequencies of specific antibody responses in relation to the exposure rates to epitope mismatches. At present, this type of information must be considered preliminary and more studies are needed on patients with mismatched transplants.

Although successful retransplantation can now be more readily performed on highly sensitized patients, we must address the question of avoiding retransplantation altogether. The application of an HLAMatchmaker-based determination of permissible mismatches might be a step in the right direction.

Rene J. Duquesnoy
Professor of Pathology, Immunology and Surgery, Clinical Consultant HLA and Histocompatibility Testing
University of Pittsburgh Medical Center
Pittsburgh, PA
USA
E-mail: duquesnoyr@msx.upmc.edu

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