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INVITED COMMENTARY

Virtual PRA replaces traditional PRA: small change but significantly more justice for sensitized patients

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Presensitized kidney graft recipients with alloantibodies against human leukocyte antigens (HLA) in their serum generally have two major disadvantages: (i) inferior graft outcome and (ii) fewer organ offers due to frequently positive (real and virtual) crossmatch results. To equalize these disadvantages, the 'mismatch probability' was introduced into the kidney allocation system of Eurotransplant (ET) in 1996. Hereby, the probability of receiving a well-matched kidney offer with 0–1 HLA-ABDR mismatches based on 1000 kidneys offered is calculated, considering recipient and donor HLA typing, recipient and donor blood groups, and the recipient's panel reactive antibodies (PRA). While, for example, a well-matched kidney with 0 HLA-ABDR mismatches enters into the point score during kidney allocation with up to 400 points and waiting time is considered with 32.85 points per year, 'mismatch probability' is currently rather underscored with a maximum of 100 points; especially in Germany, this leads, due to low rates of deceased-donor organs, to significantly prolonged waiting times in presensitized patients.

Panel reactive antibody screening is performed in the HLA laboratories quarterly to identify patients on the waiting list who are sensitized to donor HLA antigen alleles. In the traditional complement-dependent cytotoxicity (CDC)–PRA assay, the serum of the patient is tested against a panel of HLA-typed lymphocytes from randomly chosen blood donors that represents the donor population. PRA is expressed as a percentage between 0 and 99 and reflects the proportion of donor population to which the tested person is expected to react during the pretransplant crossmatch procedures. If the serum reacts only with cells that carry certain HLA antigens, also the specificity of the patient's HLA antibodies can be determined. In the ELISA and Luminex® (Austin, TX, USA) versions of the PRA testing, purified HLA molecules instead of lymphocytes are used in the composition of the panel.

One significant problem of PRA value has been its great variability [1]. Usage of laboratory-specific cell panels results in different PRA values with the same serum. More sensitive antibody test systems, such as ELISA and Lumin-

ex®, give higher PRA values than CDC, and usage of IgM-destroying agent dithiothreitol or HLA class I and class II antigen-carrying B-cell panels as more sensitive targets than only HLA class I antigen-carrying T-cell panels brings additional variability. Furthermore, calculation of total PRA is difficult if a patient, for example, has 60% PRA in class I and 80% PRA in class II antibody testing. An even more severe problem is that ET centers are currently allowed to report, even in the absence of as unacceptable reported HLA antibody specificities, high PRA values from sensitive testings. This means that, without excluding any organ offers, higher 'mismatch probability' scores can be achieved.

Panel reactive antibodies may further be distinguished in actual PRA (aPRA) representing the PRA value of the most recent pretransplant serum sample and peak PRA (pPRA) representing the highest PRA value from all tested pretransplant samples. To have a more uniform and reliable parameter for sensitization, a calculated or virtual PRA (cPRA or vPRA) was introduced. In ET, the vPRA value is planned to replace the percent PRA value in the 'mismatch probability' calculation from 1 January 2016. vPRA is calculated by considering the phenotype frequency of as unacceptable defined HLA alleles in the ET donor population. Because the specificity of the antibodies instead of the serum's reaction with a panel is the basis of the calculation, vPRA is expected to give a more accurate estimate of transplantability for most patients. Moreover, vPRA will increase the quality of antibody screening and improve graft outcome by forcing the centers to define the specificity of antibodies more precisely. Otherwise, their patients will be at disadvantage by receiving less 'mismatch probability' scores.

While cPRA was introduced by the United Network of Organ Sharing in 2009 [2], the determination of 'unacceptables' has been part of the ET organ allocation system already since the 1980s, however, independent from PRA calculation, as a measure to prevent positive crossmatches. With the introduction of vPRA in ET, these two measures will now be combined.

Due to the usage of different antibody detection systems and risk-based treatment procedures, variations in the determination of vPRA will still remain. Therefore, uniform guidelines for the determination of as unacceptable defined HLA antibody specificities are required to bring real equity into the allocation system. Such an attempt had only recently been made by the German Society for Immunogenetics DGI [3]. Instead of a maximum of 100 points that results from the calculation of 'mismatch probability', introduction of a more linear, donor frequency-adjusted allocation score would further enhance the justice.

As a note of caution, the term vPRA, although related, should not be mixed up with the term virtual crossmatch. Both terms are based on the specification of the patient's antibodies and determination of 'unacceptables'. vPRA is a parameter that is relevant for the calculation of the 'mismatch probability' allocation score, whereas virtual crossmatch describes a procedure in which organ offers with HLA antigens that are expected to cause a positive crossmatch with the recipient's serum are excluded by the computer of the allocation system without performing a real crossmatch.

In the current issue of Transplant International, Huber *et al.* investigated in a timely written article the association of vPRA, pPRA, and aPRA with long-term kidney allograft outcome [4]. vPRA and pPRA were found to be better predictors of long-term graft survival than aPRA. Despite several shortcomings, such as the comparison of results from two different eras of PRA testing and that the vPRA calculation did not cover antibodies against HLA-C, HLA-DQ, or HLA-DP, this is a useful effort to check whether the introduced vPRA value is at the same time a clinically meaningful parameter. However, rather than the better outcome prediction, the main advantage of vPRA over traditional pPRA or aPRA remains the better prediction of organ offers with negative crossmatch results and the estimation of the individual patient's waiting time. This issue, however, was not addressed (and could not be addressed) by Huber *et al.* and requires prospective studies or modeling using donor and recipient populations.

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