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Should epitope-based HLA compatibility be used in the kidney allocation system?

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ABSTRACT

The new kidney allocation system (KAS) still applies donor-recipient HLA compatibility mostly at the antigen level and although some four-digit alleles have been included. This system is used to record unacceptable mismatches for sensitized transplant candidates with serum HLA antibodies. Since the reactivities of such antibodies are specifically associated with epitopes rather than HLA antigens, a more scientifically accurate assessment of mismatch acceptability could be based on epitopes. HLA class I and class II epitope specificity analyses can now be readily performed with serum antibody assays with single allele panels. This report describes an epitope-based HLA compatibility system for KAS and involves recipient and donor HLA typing at the four-digit allele level. It focuses on sensitized patients who have serum antibodies specific for HLA epitopes that can be entered as unacceptable mismatches in the transplant candidate database. Newly developed software programs could readily identify compatible HLA types.

1. Introduction

After many years of deliberation and consensus-building, a new kidney allocation system (KAS) was implemented late 2014 by the United Network for Organ Sharing (UNOS) [1]. Its goals are to improve longevity matching between donor kidneys and recipients and promote transplant access for historically disadvantaged subpopulations including highly sensitized patients. The probability of a HLA-compatible donor for such candidates can be assessed with a Calculated Panel-Reactive Antibody (CPRA) which reflects a percentage of potential donors with unacceptable antigens [2].

During the first year of KAS, the annual number of deceased donor transplants increased by 4.6% over the previous year [3]. KAS has increased access to transplantation for recipients disadvantaged by antibody sensitization. About 8% of patients on the waiting list have 99–100% CPRA. Before KAS, they received just 2.5% of transplants, but this rose to 13.4% after KAS. This resulted in a decrease of 1000 such highly sensitized candidates on the waiting list. Transplant rates changed little for CPRA 95–98% recipients but declined for CPRA 80–89% recipients, from 6.8% to 2.7%. The remaining CPRA groups showed moderate declines. After KAS, zero-ABDR mismatched transplants fell from 8.2% to 4.7% and zero-DR mismatched kidneys decreased from 19.8% to 16.8% [3]. Of course, a much longer time is needed to evaluate the KAS effect on transplant outcome.

2. HLA mismatch acceptability strategies in KAS

The HLA matching algorithm of UNOS is based on a list of HLA antigens recognized by the World Health Organization (WHO) Nomenclature Committee. Over a period of more than three decades, HLA compatibility criteria continued to change because of improved serological definitions of HLA antigens and the identification of "splits" or subtypes of HLA antigens. They led to new criteria for the compatibility algorithm including so-called matching equivalences between antigenic types. Molecularly based HLA typing methods improved the definitions of serologically defined antigens and recently, the HLA compatibility algorithm began to include selected four-digit alleles believed to represent unique antigens not recognized by the WHO serologic nomenclature. For instance, A9 was split into A23 and A24 whereas two A24 alleles A*24:02 and A*24:03 are now being used for matching purposes. DR2 was split into DR15 and DR16 whereas three DR15 alleles are listed: DRB1*15:01, DRB1*15:02 and DRB1*15:03.

KAS has updated criteria for HLA compatibility which besides the traditional HLA-A, HLA-B and HLA-DR loci now also include the HLA-C, HLA-DQA,B and HLA-DPB loci. For each locus, the WaitList[SM] entry page of the UNOS database has tables on which

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one can record unacceptable antigens for sensitized patients. They can be selected from lists of broad and split HLA antigens and selected 4-digit HLA alleles. For each of them there are so-called Donor Equivalent Antigens that must be avoided in the HLA types of potential donors. Supplemental Tables 1–3 describe details.

For instance, when HLA-A1 is listed as an unacceptable antigen, the table only displays HLA-A1 as unacceptable. However, when HLA-A2 is unacceptable, the table lists A2, A0201, A0202, A0203, A0205 and A0206 as donor equivalents and, therefore, unacceptables. The system becomes more complicated for A9 for which A9, A23, A24, A2402 and A2403 are listed as unacceptable donor equivalent antigens and for B5 for which B5, B51, B5101 and B5102 are listed (surprisingly, B52 is not listed although this antigen together with B51 is a split of B5). The HLA-DR table lists DR1, DR0101 and DR0102 but not DR0103 as donor equivalent antigens for the unacceptable DR1. Altogether, the system of antigen equivalents is confusing and needs to be revised.

3. Exclusive use of HLA alleles in unacceptable mismatching

The criteria for unacceptable HLA antigen equivalences are based on a mixture of old and new HLA typing information. Current molecularly based HLA typing data at the antigen level do not consider anymore broad specificities such as A10, A19, A28, B5 and DR6 because their splits can now be readily determined. Therefore, one must raise the question whether they should be maintained on the list of unacceptable antigens. Moreover, currently used serum testing methodologies determine antibody-reactivity with single four-digit HLA alleles.

For instance, many single allele panels used for antibody testing have just one A1 allele, namely A*01:01. A positive reaction would render A1 as unacceptable but in reality A*01:01 should be listed. The antibody testing kit might have several A2 alleles including A*02:01, A*02:03 and A*02:06. A positive reaction with all of them might suggest that the A2 antigen is an unacceptable mismatch but would it be better to list just the reactive A2 allele as unacceptable? Moreover, some alleles corresponding to the same HLA antigen react with a given serum but others are non-reactive. Typical examples are the A*24:02 and A*24:03 of A24 and B*44:02 and B*44:03 of B44. Such cases raise uncertainties about the mismatch acceptability of a HLA antigen.

Since mismatch acceptability is now determined with modern serum screening methods with four-digit allele panels, the antigen equivalences tables should list alleles rather than antigens. This means that A1 becomes A*01:01, the five A2 alleles *A*02:01, A*02:02, A*02:03, A*02:05 and A*02:06 remain but the A2 antigen would be excluded, A3 becomes A*03:01, etc. Antigens such as A9 should be removed because there are no A9-annotated alleles. A*23:01 (rather than A23), A*24:02 and A*24:03 should be used instead. There are also no A10-annotated alleles and the associated A25, A26, A34 and A66 antigens should be replaced with A*25:01, A*26:01, A34:01, A*34:02, A*66:01 and A*66:02; the latter four alleles are already listed in the antigen equivalences table for HLA-A.

Supplemental Tables 1–3 demonstrate how a replacement of the current system based on HLA antigen equivalents by an allele-based system will make the unacceptable mismatch algorithm much easier to manage. Such system is consistent with and dependent on the concept that sensitized recipients and potential donors be typed at the four-digit allele level [4]. The HLA types of such donors may consist of alleles that are listed in the unacceptable mismatch tables. Then, it seems quite easy to determine if the donor-recipient combination is acceptable or unacceptable.

However, the unacceptable mismatch tables would be limited to alleles that are used in the antibody screening assays. For instance, most HLA-ABC kits have fewer than 100 alleles although more 8000 class I alleles have been identified and the list is still growing. Given the increasing racial and ethnic diversity of the US population, one would expect more frequent occurrences of non-panel HLA alleles in transplant donors. How does one determine the mismatch acceptability of an untested donor allele not listed in the unacceptable mismatch table? This question can especially create a dilemma if two or more alleles corresponding to a given HLA antigen have been assigned differently in terms of mismatch acceptability.

4. HLA epitope-specific antibody analysis

This problem can be solved by applying the principle that HLA antibodies are specific for epitopes [5,6]. Each allele consists of a string of epitopes that can be classified by eplets, i.e. small configurations of polymorphic amino acid configurations on the HLA molecular surface. Certain epitopes specifically associated with antibody reactivity are solely defined by single eplets and others require combinations of eplets with nearby residue configurations, they are referred as eplet pairs.

The clinical relevance of epitope-based matching should of course, only apply to epitopes that have been experimentally verified with informative antibodies. The HLA Epitope Registry (http://www.epregistry.ufpi.br) has for each locus a list of epitopes specifically associated with antibody reactivity. The website now includes a downloadable PDF file "EpiPedia of HLA" which describes the experimental evidence of HLA epitopes specifically associated with antibody reactivity. In our experience, the HLAMatchmaker antibody analysis programs (Version 2.0 downloadable from www.HLAMatchmaker.net) have shown that the reactivity of more than 90% of post-pregnancy sera can be explained with epitopes that have been specifically associated with antibody reactivity [7–9]. Thus, considerable progress has been made in defining HLA epitope repertoires but more studies are needed. The www.HLAMatchmaker.net website has now a downloadable Excel document "Five Maps of HLA Epitopia" which describe the sequence locations of eplets that correlate with antibody specificity and polymorphic residues as potential candidates defining additional epitopes. These maps can be used in navigating the continents of HLA Epitopia while searching for newly antibody-defined epitopes [10].

5. Antibody-reactive epitopes and mismatch acceptability at the allele level

In this section, an underlying assumption is that any and all HLA alleles carrying the same epitope as one defined to be unacceptable in a pre-transplant patient serum should also be considered. One could also call an epitope that is specifically associated with antibody reactivity as an unacceptable mismatch and this consideration offers several advantages in the management of the sensitized transplant candidate. The identification of epitope specificities will increase our understanding of complex serum reactivity patterns often seen for highly sensitized patients. Some sera should be investigated further with absorption-elution studies with selected alleles. The HLA typing information of the patient and preferably the immunizing donor(s) will greatly facilitate the epitope specificity analysis.

Since most sera have antibody reactivities associated with small numbers of epitopes, it would be rather easy for histocompatibility testing laboratories to enter such unacceptable epitopes into the WaitList^{SM} entry page of the UNOS database. A dedicated software