American Journal of Transplantation 2015; XX: 1–8
Wiley Periodicals Inc.

doi: 10.1111/ajt.13167

Personal Viewpoint

Personal Viewpoint: Should HLA Mismatch Acceptability for Sensitized Transplant Candidates Be Determined at the High-Resolution Rather Than the Antigen Level?

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Defining HLA mismatch acceptability of organ transplant donors for sensitized recipients has traditionally been based on serologically defined HLA antigens. Now, however, it is well accepted that HLA antibodies specifically recognize a wide range of epitopes present on HLA antigens and that molecularly defined high resolution alleles corresponding to the same low resolution antigen can possess different epitope repertoires. Hence, determination of HLA compatibility at the allele level represents a more accurate approach to identify suitable donors for sensitized patients. This approach would offer opportunities for increased transplant rates and improved long term graft survivals.

Abbreviations: cPRA, calculated panel reactive antibody; NMDP, National Marrow Donor Program; SAB, single allele bead; UNOS, United Network for Organ Sharing

Received 28 July 2014, revised 19 October 2014 and accepted for publication 11 November 2014

Introduction

Many patients awaiting transplantation are considered sensitized because their sera have antibodies that react with HLA antigens which are then categorized as unacceptable mismatches. Highly sensitized transplant candidates represent a clinical enigma: because it is difficult to find a suitably matched donor they must incur much longer waiting times and when they receive a transplant many are at greater risk for posttransplant complications. Sera from these patients have antibodies with very broad HLA reactivity patterns. Whereas a calculated panel reactive antibody (cPRA) value of >80% was once considered a high degree of HLA sensitization, the most disadvantaged candidates have cPRAs of >98%.

Multicenter transplant organizations such as the United Network for Organ Sharing (UNOS), Eurotransplant,

theNational Health Service Blood and Transplant program in The United Kingdom and Canadian Blood Services-Organ Donation and Transplantation, have organ allocation protocols designed to give preference to highly sensitized patients to increase their chances of receiving a compatible organ. The selection of donors has traditionally considered mismatch acceptability at the HLA antigen (two-digit) level as determined from serum antibody reactivity patterns with HLA panels. Many laboratories currently use sensitive HLA antibody detection assays with single allele bead (SAB) panels but the reactive alleles are converted to antigen equivalents which are then recorded in registries as unacceptable mismatches. These panels have often two or more alleles corresponding to the same antigen. This can create a dilemma in the interpretation of mismatch acceptability at the antigen level when corresponding alleles have different reactivity with patient's serum antibodies. This includes circumstances whereby the recipient's HLA type includes one allele of an antigenic group yet the recipient has antibody reactivity against a different allele within that same group. Moreover, how does one handle the mismatch acceptability of an allele not present in the SAB panel? Would conversion of an HLA allele to a two-digit antigen be without any risk to the recipient?

HLA alleles have better defined antibody-reactive epitope repertoires

About 30 years ago, Rodey and co-workers began to report that high PRA sera from sensitized transplant patients have generally antibodies against one or a few so-called public epitopes which have rather high frequencies in the donor population (1–3). Molecular modeling and amino acid sequence comparisons have permitted structural descriptions of HLA epitopes (4–9). There is an extensive literature about the experimental documentation of structurally defined epitopes reacting with specific antibodies produced in people sensitized by a transplant or during pregnancy. Many antibody-verified epitopes have been listed on the HLA Epitope Registry website (http://www.epregistry.com.br); this project is a work-in-progress and we expect that additional antibody-verified epitopes will be identified. Epitopes are distributed across the HLA molecular surface and the degree of mismatching depends on the extent of epitope differences between HLA alleles of the donor and recipient. Alleles expressing epitopes that are recognized by antibodies from sensitized transplant candidates can be deemed unacceptable mismatches whereas alleles without those epitopes would be considered as acceptable mismatches. Three tables illustrate the importance and advantages of considering allele mismatches rather than antigen mismatches.

Table 1 has examples of how alleles corresponding to the same antigen can have different reactivity with epitope-specific antibodies. These HLA class I epitopes have been experimentally well documented with specific antibodies and recorded in the HLA Epitope Registry website as described in a recent publication (10). HLA epitopes are annotated with

Table 1: Examples of antibody-reactive epitope expression on SAB alleles corresponding to the same antigen and predictions of unacceptable and acceptable non-SAB alleles

Antibody reactive epitope	Epitope-carrying SAB alleles	Potential donor antigen	Epitope-carrying reactive SAB alleles (Unacceptable)	Non-reactive SAB alleles (Acceptable)	Predicted unacceptable non-SAB alleles	Predicted acceptable non-SAB alleles
145KHA	A*01:01,A*02:01,A*02:02,A*02:05, A*02:06,A*03:01,A*11:01,A*11:02, A*24:02,A*24:03,A*36:01, A*68:01, A*68:02,A*69:01,A*80:01	A2	A*02:01/02/05/06	A*02:03	A*02:07/10/12/13/14/16/17	A*02:19/25
166DG	A*01:01,A*23:01,A*23:02,A*24:02, A*80:01,B*15:12	A24	A*24:02	A*24:03	A*24:05/07/08/14/17/20	A*24:10/18/22
65QIA	B*07:02,B*27:03,B*27:05,B*27:08, B*42:01,B*54:01,B*55:01,B*56:01, B*67:01,B*73:01,B*81:01,B*82:01, B*82:0	B7	B*07:02	B*07:03	B*07:04/05/09/10	B*07:08/13/16
21H	C*02:02,C*02:10,C*03:02,C*03:03, C*03:04,C*04:03,C*15:02,	Cw4	C*04:03	C*04:01/02	C*04:06/16	C*04:04/05/07/08

standard single letter amino acid codes in molecular sequence positions and they are expressed on different groups of SAB alleles. For instance, 145KHA is a high-frequency antibody-verified epitope shared between 15 HLA-A SAB alleles (Table 1). Anti-145KHA antibodies react with the HLA-A2 alleles A*02:01, A*02:02, A*02:05, and A*02:06 but not with A*02:03 which lacks 145KHA. Similarly, anti-166DG antibodies react with A*24:02 but not with A*24:03 and anti-65QIA antibodies react with B*07:02 but not with B*07:03. Antibodies against HLA-C epitopes such as 21H may also react differently with alleles corresponding to the same antigen; in this case, anti-21H antibodies react with C*04:03 but not with C*04:01 and C*04:02.

How is this information used in the classification of potential donors whose HLA typing is limited to the two-digit antigen level? A conservative approach would be to consider all such antigens as unacceptable but under such circumstances the patient might be denied an opportunity of a transplant with a suitable allelic mismatch. This situation becomes more complicated when the patient's own phenotype contains one allele while the patient has antibody against a different allele of the same antigen group. For instance, a patient who types as A*24:03 may have 166DG-specific antibodies that react with the 166DG-carrying A*24:02 although at the antigen level, A24 would be considered a match.

Conversely, such antigens might be considered acceptable mismatches but then there is an increased likelihood of a positive crossmatch if the donor has the unacceptable allele and this could lead to a cancelled transplant.

Several reports have been published describing unexpected allele reactivity with transplant patient sera. For instance, a kidney transplant recipient who typed for B*44:03 had antibodies that reacted with B*44:02; they were specific for the 156DA-defined epitope presented by the immunizing C*07:04 allele and shared with B*44:02 and a few other HLA-B alleles (11). Two patients who typed as B*13:02 had antibodies that reacted with all Bw4-carrying alleles except B*13:01 and B*13:02 (12). These antibodies recognized a specific epitope defined by 145R paired with the Bw4-associated 82LR. A recent report describes a case of an Africa—American transplant candidate who typed as B*27:05 and had antibodies against an epitope shared between all Bw4-carrying alleles except B*27:05 and B*44:02 (13). We are aware of other similar findings and all these cases illustrate how difficult it would be if mismatch acceptability were solely determined at the antigen level.

SAB panels are generally limited to less than 100 alleles. If a donor possesses HLA alleles present in these panels, compatibility can be readily assessed even without knowledge of epitope-specific antibody reactivity patterns. However, the assessment of compatibility becomes more challenging when a potential donor types for HLA alleles not present in the SAB panel. Antigen-based typing of such donors may not be adequate to assess HLA compatibility. The two columns on the right of Table 1 show examples of potential donor antigens with non-SAB alleles for which it can be predicted based on a structural epitope analysis, whether or not they will react with the corresponding antibody. This approach permits a distinction whereby alleles not represented on the SAB panel can be predicted as unacceptable or acceptable mismatches. For instance, for a patient with 65QIA-specific antibodies which react with the 65QIA-bearing B*07:02 in the SAB panel; 65QIA-bearing B7 alleles such as B*07:04, B*07:05, B*07:09, and B*07:10 can be considered unacceptable mismatches but B*07:03, B*07:08, B*07:13, and B*07:16 would be acceptable because they lack the 65QIA epitope.

Table 2 displays additional examples of common antibody-verified epitopes that are shared between groups of epitope-carrying SAB alleles. In each case, two potential donor antigens have been selected, one seems to be an unacceptable mismatch and the other might be considered an acceptable mismatch. However, corresponding non SAB alleles have structural epitope differences that would affect their mismatch acceptability. Thus for the B58 antigen, the 62GE epitope-bearing B*58:02 and B*58:06 alleles should be considered unacceptable mismatches for patients with anti-62GE antibodies but B*58:04 would be acceptable as it does not bear 62GE. A*24:02 and A*24:03 in the SAB panel do not react with anti-62GE antibodies and they are acceptable mismatches. For the A24 antigen, all corresponding non-SAB alleles except the 62GE-bearing A*24:08 would be acceptable mismatches. Sera with anti-76AN antibodies react with A*26:01 and would be predicted to react with four other 76AN-carrying A26 alleles (A*26:02, A*26:07, A*26:08, and A*26:09) then identified as unacceptable mismatches. In contrast, three A26 alleles (A*26:03, A*26:05, and A*26:06) can be considered acceptable mismatches because they lack the 76AN epitope. The 76AN-carrying A*24:04 non-SAB allele is predicted as an unacceptable mismatch. Predictions of mismatch acceptability of non-SAB alleles can also be made for high-frequency epitopes such as the antibody-verified 76ESN. Table 2 shows only a representative set of alleles with last digits under 10; most antigens have many more corresponding alleles.

The prediction of mismatch acceptability of non-SAB alleles is solely based on the sharing of epitopes with SAB alleles tested for their reactivity with patient's serum. Epitope-specific antibodies react generally with a diverse group of multiple SAB alleles that share the epitope specifically recognized; alleles that lack such epitope are nonreactive. Because of the perfect correlations ($R = 1.0$) between antibody reactivity with the SAB panel and the epitope specifically recognized, it seems that the identification of the amino acid structure corresponding to the epitope on non-SAB alleles offers a reasonable prediction of mismatch acceptability. Such predictions can be experimentally

Table 2: Prediction of mismatch acceptability of non-SAB alleles corresponding to selected donor HLA antigens for patients with antibodies specific for the 62GE, 76AN and 76ESN defined epitopes

Epitope	Epitope-carrying SAB alleles	Donor antigen	Predicted unacceptable or acceptable non-SAB alleles
62GE	A*02:01,A*02:02,A*02:03,A*02:05,A*02:06,B*57:01,B*57:03,B*58:01	B58 (unacceptable?)	B*58:02/06 NOTB*58:04
		A24 (acceptable?)	A*24:04/05/06/07/10 NOT A*24:08
76AN	A*01:01,A*26:01,A*29:01,A*29:02,A*36:01,A*43:01,A*80:01	A26 (unacceptable?)	A*26:02/07/08/09 NOT A*26:03/05/06
		A24 (acceptable?)	A*24:05/06/07/08/10 NOT A*24:04
76ESN	B*07:02,B*07:03,B*08:01,B*14:01,B*14:02,B*15:01,B*15:02, B*15:03,B*15:10, B*15:11,B*15:12,B*15:18,B*18:01,B*27:08, B*35:01,B*35:08,B*39:01,B*39:05, B*40:01,B*40:02,B*40:06, B*41:01,B*42:01,B*45:01,B*48:01,B*50:01,B*54:01, B*55:01, B*56:01,B*67:01,B*78:01,B*81:01,B*82:01,B*82:02	B8 (unacceptable?)	B*08:04/05/07/09/10 NOT B*08:02/03
		B44 (acceptable?)	B*44:04/05/06/08/10 NOT B*44:09

verified if allele-based typing becomes available for sensitized patients and their prospective donors.

Selection of alleles expected to be present in transplant donor populations

More than 8000 class I alleles are listed on the World Health Organization HLA Nomenclature website http://hla.alleles.org. A practical approach for a matching algorithm is to consider only those alleles expected in the potential donor pool; rare alleles must be excluded. An analysis of allele frequency data on the Allele Frequencies website (http://www.allelefrequencies.net) (14) has identified alleles with frequencies higher than 0.5% in at least one of the population groups consisting of minimally 500 individuals and classified as American Caucasian, African–American, Hispanic American, Asiatic American, European Caucasian, Chinese and Japanese. One of the authors of this paper (RJD) has grouped such alleles according to selected corresponding antigens and conducted amino acid sequence alignment analyses to identify amino acid differences. It is reasonable to consider that these amino acid differences could translate into significant structural differences that would have the potential to be recognized as distinct epitopes.

Table 3 shows residue differences for alleles corresponding to two HLA-A antigens (A2 and A24) and two HLA-B antigens (B27 and B35). Alleles on SAB panels are annotated with an asterisk and it should be noted that several alleles (A*02:03, A*02:10, A*24:03, and B*27:08) have already been recorded as WHO-recognized serological specificities (A203, A210, A2403, and B2708, respectively) on the http://hla.alleles.org website. Positions in boxes represent residues on the molecular surface where they have the potential to make direct contact with antibodies.

Certain alleles within each antigen group have very few residue differences in sequence positions below the molecular surface and cannot make direct contact with antibodies. For instance, A*02:01 has only a single residue difference with A*02:04 (97R vs. 97M) and with A*02:07 (99Y vs. 99C) but there are three residue differences with A*02:03 (149A, 152V, 156L vs. 149T, 152E, 156W) and A*02:10 (9F, 99Y, 107W vs. 9Y, 99F, 107G). The latter two alleles have been recognized as serological specificities: A*02:03 has a major epitope difference with A2 involving position 149 (see Table 1), whereas A*02:10 has 107G rather than 107W which defines an epitope shared between the other A2 alleles and A*69:01. Similarly, B*27:05 differs by only one residue from B*27:09 (116D vs. 116H) but varies by three residues from B*27:04 (77D, 152V, 211A vs. 77S, 152E, 211G). B*27:05 (B27) has four different residues in the 77–83 region when compared to B*27:08 which is analogous to the B2708 serological specificity. Thus, within a given antigen group, there are certain alleles that are structurally very similar and would have identical

Table 3: Amino acid residue differences between HLA-A2, -A24, -B27 and -B35 alleles with greater than 0.5% frequencies in one or more common population groups of potential transplant donors

Position	9	43	66	73	74	95	97	99	107	149	152	156
A*02:01* (A2)	F	Q	K	T	H	V	R	Y	W	A	V	L
A*02:02*	–	R	–	–	–	L	–	–	–	–	–	W
A*02:03* (A203)	–	–	–	–	–	–	–	–	–	T	E	W
A*02:04	–	–	–	–	–	–	M	–	–	–	–	–
A*02:05*	Y	R	–	–	–	L	–	–	–	–	–	W
A*02:06*	Y	–	–	–	–	–	–	–	–	–	–	–
A*02:07	–	–	–	–	–	–	–	C	–	–	–	–
A*02:08	Y	R	N	–	–	L	–	–	–	–	–	W
A*02:10* (A210)	Y	–	–	–	–	–	–	F	G	–	–	–
A*02:11	–	–	–	I	D	–	–	–	–	–	–	–
A*02:12	–	–	–	–	–	–	–	–	–	–	–	Q
A*02:17	–	–	–	–	–	L	M	F	–	–	–	–
A*02:20	–	–	N	–	–	–	–	–	–	–	–	–

Position	3	7	62	65	70	76	79	80	81	82	83	114	116	163	166	167
A*24:02* (A24)	H	Y	E	G	H	E	R	I	A	L	R	H	Y	T	D	G
A*24:03* (A2403)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	E	W
A*24:04	–	–	–	–	–	A	G	T	L	R	G	–	–	–	–	–
A*24:07	–	–	–	–	Q	–	–	–	–	–	–	–	–	–	–	–
A*24:08	Q	–	G	R	–	–	–	–	–	–	–	–	–	–	–	–
A*24:10	–	–	–	–	–	–	–	–	–	–	–	–	–	R	E	W
A*24:17	–	–	–	–	–	–	–	–	–	–	–	R	D	–	–	–
A*24:20	Q	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
A*24:25	–	C	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Position	59	77	80	81	82	83	97	113	114	116	131	152	211
B*27:05* (B27)	Y	D	T	L	L	R	N	Y	H	D	S	V	A
B*27:02	–	N	I	A	–	–	–	–	–	–	–	–	–
B*27:03	H	–	–	–	–	–	–	–	–	–	–	–	–
B*27:04	–	S	–	–	–	–	–	–	–	–	–	E	G
B*27:06		S				–	–		D	Y	–	E	G
B*27:07	–	–				–	S	H	N	Y	R	–	–
B*27:08*(B2708)	–	S	N	–	R	G	–	–	–	–	–	–	–
B*27:09	–	–	–	–	–	–	–	–	–	H	–	–	–

Position	67	94	95	97	103	109	114	116	152	156	194
B*35:01*(B35)	F	I	I	R	L	L	D	S	V	L	V
B*35:02	–	–	–	–	–	F	N	Y	–	–	–
B*35:03	–	–	–	–	–	–	–	F	–	–	–
B*35:04	–	–	–	–	–	–	N	Y	–	–	–
B*35:05	–	T	L	S	–	–	–	–	–	–	–
B*35:08*	–	–	–	–	–	–	–	–	–	R	–
B*35:12	–	–	–	–	V	–	N	Y	–	–	–
B*35:14	–	–	–	–	–	–	–	–	E	W	–
B*35:17	–	–	–	S	V	–	–	–	–	–	–
B*35:20	S	–	–	–	–	–	–	–	–	–	–

*Alleles in single allele bead (SAB) panels are annotated with an asterisk; the equivalent serological antigen is also listed. Antibody-accessible sequence positions on the molecular surface are in boxes.

epitope repertoires whereas other alleles are structurally more different and might carry distinct epitopes which affect their mismatch acceptability.

Observations with HLA-DR, -DQ, and -DP epitope-specific antibodies mimic the data for class I epitope specific antibodies (data not shown). Recent studies demonstrate the clinical relevance of determining epitope specificities of class II antibodies and the role of epitopes in class II matching (15–20); defining compatibility at the allele level is beneficial for sensitized transplant candidates with class II reactive antibodies (21).

What are the advantages of allele-based determination of mismatch acceptability?

These findings illustrate that high resolution typing focused on alleles offers a more precise approach than antigen typing to assess mismatch acceptability for sensitized patients. The traditional approach of antigen-based mismatch acceptability determination might be sufficient for transplant programs that allocate organs from donors in a racially and ethnically homogenous population as it seems more likely that a given HLA antigen is equivalent to one allele. Nowadays, much more diversity within populations of organ donors and recipients has led to an increase in the number of alleles seen for each antigen. This means to a greater likelihood for errors when attempting to assess mismatch acceptability. The clinical consequence is that sensitized patients might be denied a suitable organ or might receive a transplant with a higher risk of rejection and possible failure. Furthermore, unexpected positive crossmatches at the receiving transplant centers could be predicted and avoided if patient and donor were typed at the allele level. With broader geographic sharing and increased priority for the most highly sensitized recipients the predictability of virtual cross-matching for these patients is all the more vital given the logistic consequences of shipping donor organs.

Can allele-based determination of mismatch acceptability be applied in the clinical setting?

Although there is agreement on the clinical utility of high-resolution typing of patients and donors and to use alleles in the listing of unacceptable or acceptable mismatches for sensitized patients, there is not surprisingly, disagreement within the transplant community on its application at a practical level. The main arguments focus on cost, time constraints, and lack of funding to pilot the change.

Most transplant programs have rather high proportions of sensitized patients. In UNOS, about 40% of patients on the waiting list have unacceptable antigen records; this suggests that many sensitized patients could benefit from high-resolution typing which permits a more accurate assessment of mismatch acceptability. While we anticipate a higher successful transplant rate we recognize that a cost to benefit analysis is needed to assess the practical usefulness of allele-based allocation.

One concern is that high-resolution typing will have a minimal impact on highly sensitized patients with cPRA values close to 100%. Epitope specificity analyses are often difficult because sera react with almost every allele in the panel. There is now increasing evidence that highly reactive antibodies are often specific for high-frequency epitopes. The website-based HLA Epitope Registry (http://www.epregistry.com.br) has several examples of such antibody-verified class I and class II epitopes. The resolution of epitope specificity of highly reactive sera will require additional testing including absorption-elution studies with informative alleles so that more precise data can be generated for the identification of unacceptable mismatches for highly sensitized patients. Epitope specificity determination offers a new window of opportunity of a transplant and HLA typing at the allele level will permit a clearer view.

Another concern is the turn-around time of high-resolution testing of deceased donors. Most if not all histocompatibility testing laboratories are already performinghigh-resolution HLA typing and with newer technological advances, typing results can now be readily obtained within a few hours after test setup similar to antigen-based typing. High-resolution typing kits could be designed to include alleles expected in patients and donors in a transplant program. This can be achieved through collaborative interactions with the manufacturers of the HLA typing kits. In addition, allele-level HLA assignments can be based on statistical imputation using a set of statistical and population genetics inferences with knowledge of haplotype frequencies according to race as recently reported (22). This approach is routinely used by the Be The Match® Registry of the National Marrow Donor Program (NMDP) for donor selection. In most cases this method permits accurate allele determinations and ambiguous assignments could be resolved by high-resolution typing as needed.

There is also some skepticism about the clinical usefulness of what amounts to a paradigm shift. The term ''antigen'' conveys an entity that generates an immune response whereas some transplant professionals believe that the term ''allele'' implies less antigenicity. The reality is that HLA antibodies specifically recognize epitopes and that alleles offer better descriptions of epitopes than antigens. Another point of view is that each antigen has only one or two common alleles; other alleles are so rare that it seems extremely unlikely that a patient has developed an antibody to a rare allele. We must point out that rare alleles can share a given epitope with common alleles. Such rare alleles would react with antibodies against that epitope although the patient has never been exposed to them.

Laboratories are generally required to screen sera for HLA antibodies with SAB panels that contain beads coated with single alleles. Many of them have begun to analyze serum reactivity for epitope-specific antibodies and this can now also be done with dedicated software programs supplied

commercial vendors of antibody testing kits. Unacceptable alleles can be determined from epitope specificities of antibodies. Another approach would be to identify acceptable epitope mismatches on SAB alleles based on a lack of antibody reactivity in patient's serum; any other allele which is mismatched only for such epitopes could be considered acceptable. One should be aware that some SAB alleles may have unexpected non-HLA specific reactivity with patient's serum. This raises the question whether such alleles should be considered unacceptable mismatches or is this reactivity clinically irrelevant? Recent technical and procedural modifications of single bead assays have diminished this non-HLA specific reactivity thereby improving the identification of HLA epitope-specific antibodies.

The total number of alleles selected for mismatch acceptability determination depends on their frequencies in the organ donor population. As a guideline, we have considered alleles with frequencies of greater than 0.5% in at least one major population group reported on the http://www.allelefrequencies.net website. The examples in Table 3 must be considered provisional and more analyses of frequency data are needed. A recent study has identified 237 HLA class I alleles (23), the website http:/igdawg.org has more details. Furthermore, large populations of allele-typed potential donors in various bone marrow transplant registries worldwide offer ready opportunities to identify alleles present in populations covered by different transplant programs. For instance, NMDP has HLA allele frequency and haplotype data for more than 6 million subjects categorized at race levels. Such large numbers should give reasonable estimates of allele frequencies expected in organ donors in UNOS. Similarly, allele frequency data in bone marrow donor registries in other geographic locations as well as data on the www.allelefrequencies.net website will permit the identification of allele repertoires in other organ transplant programs. This information would also permit cPRA determinations at the allele level.

Several alleles within a given antigen group have very few amino acid differences as illustrated in Table 3. Often enough, they occur in sequence positions not readily accessible to antibody and may not give rise to distinct epitopes. Such alleles might be considered serologically equivalent and corresponding allele strings could have similar designations as the G-groups used by NMDP in the allele matching algorithm on the https://bioinformatics.bethematchclinical.org website. Validation of this equivalence prediction can be performed prospectively.

As the field inevitably moves towards epitope based compatibility testing, this ''View point'' provides a scientific argument for the advantage of assessing HLA compatibility at the allele level. This applies not only to the HLA-A, -B, -DR (DRB1), and -DQB loci but also to HLA-C, -DRB3/4/5, -DQA, and -DP mismatches which may lead to antibodies that are deleterious to the transplanted organ.

The implementation of allele-based matching in the clinical transplant setting will raise many practical issues that require a great deal of community discussion and public comments. Such discussions should include a cost to benefit analysis to determine its feasibility in the clinical setting.

Naturally, one must consider the fairness of an allele-based compatibility schema since there are differences in allele distributions among various racial groups. However, this concern is unlikely to be significant. In fact, this proposed allele-based mismatch acceptability algorithm would facilitate the identification of suitably matched donors for minority populations by eliminating the unexpected positive crossmatches due to allele-reactive antibodies.

Conclusion

The science of histocompatibility testing has advanced considerably. High-resolution typing permits a better assessment of donor-recipient compatibility and the number of clinically relevant HLA gene loci has expanded. Our proposal is for sensitized patients in transplant programs worldwide. In an era of personalized medicine, we feel obligated to have as accurate as possible donor HLA information for all patients with different racial and ethnic backgrounds. High-resolution typing information will also offer new directions to increase our understanding of antibody responses to HLA mismatches and the clinical relevance of HLA epitope-specific antibodies in transplantation. Eventually, high-resolution typing should also be done for non-sensitized patients and an epitope-based algorithm for mismatch permissibility could be developed to prevent sensitization and this would especially benefit pediatric transplant patients. As the first step, let us switch HLA mismatch acceptability from antigens to alleles.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

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