A Lifetime Versus a Graft Life Approach Redefines the Importance of HLA Matching in Kidney Transplant Patients

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Introduction. Human leukocyte antigen (HLA) matching has been de-emphasized in the allocation of renal allografts and further discounting is planned in the new United Network of Organ Sharing kidney allocation model. An unforeseen consequence of poorer matching could be increased sensitization for candidates pursuing retransplantation.
Methods. We examined candidates listed in the United States from 1988 to 2007 from the Scientific Renal Transplant Registry (SRTR) database that were relisted after loss of a primary kidney transplant (n=15,980). The primary outcome was change in panel reactive antibody (PRA) from prior to recipient's initial transplant to the subsequent listing. Absolute change in PRA levels were examined in general linear models and the likelihood of becoming newly sensitized in logistic models.
Results. There was no appreciable change in PRA for patients receiving a first 0 HLA-A, -B, -DR, or 0 HLA-A, -B–mismatched kidney transplant; contrariwise, there was a significant increase in PRA by increasing HLA mismatch of the first transplant. Only 10% of patients became sensitized after a 0 HLA-A, -B–mismatched transplant, whereas the proportion rose up to 37% with increasing HLA mismatches. Other factors, notably younger age and African American race, also contributed to a higher PRA at relisting.
Conclusions. Although there might be a limited impact of HLA matching on acute rejection and graft survival, many patients might be negatively impacted from poor HLA matching of their first kidney transplant when needing a second transplant. This might be particularly important in patients with a long life expectancy because of the high likelihood of needing a second transplant during their lifetime.

Keywords: HLA matching, Sensitization, Retransplantation.

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With advances in immunosuppression, acute rejection (AR) rates during the first year after kidney transplantation have decreased over the last 15 years to a current incidence of 10% to 15% (*1*). There is also some evidence that late rejection rates have improved over time (*2*). As rejection rates have become more manageable, human leukocyte antigen (HLA) matching has been progressively de-emphasized by the United Network of Organ Sharing (UNOS) organ allocation policy. Initially, HLA-B matching (*3*) and, subsequently, HLA-A matching were eliminated from the algorithm to calculate prioritization for kidney allocation in the United States (*4*). In addition, HLA matching has been removed totally from the allocation scheme by the California Transplant Donor Network (*5*). In living donor transplantation, it was noted that by moving from living related to unrelated transplantation, no significant price had to be paid in terms of AR and graft survival (*6*). For deceased donor transplant recipients, the differences in graft survival by HLA matching are possibly an acceptable tradeoff, (*7*), for the goal to increase kidney allocation to minorities by de-emphasizing matching in the allocation system (*3*). In addition, kidney allocation across large geographical allocation areas can potentially make HLA matching difficult because of the competing risk of cold ischemia time (*8*). Conversely, the possibility exists that sensitized patients and retransplant patients will be penalized by policies to abolish HLA matching as a driver in the allocation system (*9*, *10*) and that is why other countries have held on to those policies.

As a consequence of changing allocation policies in the United States, in both deceased and living donor kidney transplantation, the mismatch between donors and recipients has increased each year (*11*). Although the impact of these changes on AR and graft survival has been deemed acceptable, there might be additional significant unintended and partially unexplored consequences. That is, it is possible that a more mismatched kidney transplant leads to a higher degree of allo-sensitization after transplant loss as suggested by a study from the Johns Hopkins transplant center (*12*). It has been

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known for a long time that patients with AR of their allograft can develop anti-HLA antibodies (*13*). Allo-sensitization as measured by panel reactive antibodies (PRAs) is a strong risk factor for AR and potentially graft loss of a subsequent transplant (*14*). More importantly, high PRA levels can nullify the patient's chance of getting another transplant (*12*). As the third most common cause for wait listing in the United States is a previously failed transplant (*15*), the decreased emphasis on HLA matching could have a significant impact on a large patient population in need of a repeat transplant.

In fact, it is well known that repeat transplant patients have on average significantly higher PRAs and associated longer waiting times and worse outcomes (*11*). It has been described in a brief report that better cross-reactive antigen group (CREG) matching might result in a decreased risk for sensitization, but the effect of HLA-matching from a primary transplant and subsequent change in PRA has not been investigated on a large scale (*16*). In this study, we intended to expand the existing research by investigating the question of whether more HLA mismatches (MMs) with a first transplant predispose to higher PRA at listing for a second transplant.

METHODS

The study population included patients listed for solitary kidney transplantation between the years 1988 and 2007 after a graft loss registered in the national SRTR database. For patients with multiple relistings during the study period, only the first relisting episode was used for the analyses. Patients with missing PRA levels at either interval were excluded from the study. The primary variable of interest was the change in peak PRA level from the initial transplant episode to the time of relisting. Secondary outcome measures included the proportion of newly sensitized patients at relisting (based on patients with a 0% PRA for the first transplant episode). In addition, risk factors for a change from a 0% PRA during the initial transplant episode to a PRA level greater than 30% or greater than 80% at relisting were evaluated.

A multivariate linear regression model was used to evaluate factors associated with the change in PRA levels from the initial transplant episode to relisting. This model incorporated recipient and donor age at the time of initial transplant, recipient and donor race, gender, HLA-mismatching for the initial transplant episode, donor type, primary diagnosis, recipient body mass index, and time from the initial transplant episode to the time of relisting. The impact of HLA mismatching was examined in several manners: by examining the HLA-A, -B, and -DR levels separately, by aggregating HLA-A and -B mismatching together and by examining the total number of HLA-A, -B, -DR cumulatively. Three logistic models were generated to evaluate factors associated with the likelihood for patients to become newly sensitized based on the population of nonsensitized patients (PRA=0%) during the initial transplant. The three models were generated for these patients with an event defined as a new PRA level at listing more than 0%, more than 30%, and more than 80%.

RESULTS

The initial population was 20,014 relisted candidates within the study period. Among these, 4037 had missing PRA levels at either the initial transplant episode or during relisted and were excluded from the analysis. Demographic information for the study population is listed in Table 1. Patients with missing PRA values were predominately recipients before 1996 (86%) for which this variable was not reported in the database as frequently. Fifty-three percent of the study population received their initial transplant before 1996. Deceased donor transplants were more commonly associated with missing PRA levels (21%) when compared with a living donor transplants (18%) and missing PRA levels more likely to have had a six-antigen matched transplant when compared with a mismatched transplant (24% and 18%, respectively, $P<0.01$).

TABLE 1. Study population characteristics

Second transplant candidate characteristic	N=15980 (%)
Primary transplant from deceased donor	11,370 (71)
HLA-A 0 mismatches from initial transplant	2795 (18)
HLA-B 0 mismatches from initial transplant	2369 (15)
HLA-DR 0 mismatches from initial transplant	3949 (25)
Six-antigen match from initial transplant	1095 (7)
African American race	5476 (34)
African American donor for primary transplant	2562 (16)
Female gender	6603 (41)
Diabetes as primary diagnosis	1928 (12)
Obese (BMI ≥30 kg/m^2)	2439 (20)[a]
Recipient age at initial transplant (mean±SD)	36±14
Donor age at initial transplant (mean±SD)	36±16
Months from initial transplant to relisting (mean±SD)	55±46
Peak PRA from initial listing (Q1/median/Q3)	0/3/12
Peak PRA at relisting (Q1/median/Q3)	0/11/68

[a] Missing values excluded from proportion.

HLA, human leukocyte antigen; PRA, panel reactive antibody; BMI, body mass index.

Table 2 displays factors that influence PRA levels at second listing, one of the most striking being the progressive effect of HLA mismatching from 0 to 6 antigens (Fig. 1). Additional factors with a statistically significant change in PRA were donor type, age and race, recipient gender, and time from initial transplant to relisting. Risk factors for patients to become newly sensitized at relisting are displayed in Table 3. Among this subset of patients with an initial PRA of 0% (n=6685), pediatric candidates less than 11 years of age (adjusted odds ratio [AOR]=1.28, relative to candidates 18–34), African American candidates (AOR=1.26, relative to Caucasians), patients with the longest intervals (>8 years) after initial transplant (AOR=2.05, relative to less than 2 years), and patients with higher HLA-A, -B, and -DR mismatching had greater likelihood to be newly sensitized at relisting.

A more detailed effect of HLA mismatching is shown in Figure 2. Sensitization was low or absent for patients with a 0 HLA-A, -B MM, independent of HLA-DR matching. The PRA rose significantly with either one HLA-A or -B MM, with further increases when more mismatches were present. After controlling for HLA-A, -B MMs, the DR locus had only a marginal effect. Additional analysis investigating the interac-

TABLE 2. Least-squared mean levels of changes in PRA level from initial transplant to relisting

Explanatory factor	Level	Adjusted mean % change in PRA	P[a]
Donor type	Deceased Donor	14.5	0.01
	Living Donor	16.4	
Recipient age (yr)	0–11	21.9	<0.001
	12–17	21.9	
	18–34	16.0	
	35–54	13.1	
	55–64	9.1	
	65+	10.5	
Recipient race	African American	18.3	<0.001
	Other	14.1	
	White	13.9	
Donor age (yr)	0–17	17.5	<0.001
	18–49	16.8	
	50–59	14.7	
	60+	12.6	
Donor race	African American	14.1	0.003
	Other	15.1	
	Caucasian	17.0	
Candidate gender	Female	12.4	<0.001
	Male	18.4	
Time to relisting (mo)	0–24	12.2	<0.001
	25–60	18.8	
	61–96	15.6	
	97+	15.1	
Primary diagnosis	GN	15.5	0.07
	Secondary GN/Vasculitis	14.3	
	Polycystic disease	18.7	
	Other congenital disorders	15.2	
	Diabetes	16.1	
	Interstitial nephritis	12.7	
	Neoplasms/tumors	13.3	
	Other	16.9	
	Hypertension	16.1	
Candidate BMI	Missing	15.3	0.21
	<20	15.1	
	20–24	13.9	
	25–29	15.3	
	30–34	15.5	
	35+	17.4	
Total HLA-A, -B, -DR mismatches	0	0.8	<0.001
	1	9.0	
	2	15.9	
	3	18.9	
	4	19.0	
	5	22.7	
	6	21.7	

[a] Type-III significance level of factor from multivariate linear regression model.

GN, glomerulonephritis; HLA, human leukocyte antigen; BMI, body mass index; PRA, panel reactive antiobody.

tion of HLA-A with HLA-B MMs indicates that HLA-A MMs were associated with steeper increases in PRA relative to HLA-B MMs (Fig. 3). Patients with two HLA-A MMs and no HLA-B MMs had an average PRA increase of 23%, whereas those having two HLA-B MMs only had an increase of 13%. In addition, it seems that the increases seen with two HLA-A MMs do not result in higher PRA with additional HLA-B MMs.

Examination of the proportion of patients previously nonsensitized who become sensitized (PRA>30%) showed a similar trend (data not shown). More patients were at risk of high sensitization with any HLA-A or -B MMs when compared with no mismatches, and HLA-A MMs seem to contribute more significantly to this risk. The proportion of previously nonsensitized patients that were newly sensitized based on different PRA thresholds were 51% (>0%), 34% (>30%), and 16% (>80%). The data are not displayed here, but the effect of HLA mismatching was similar on the different levels of new sensitization.

Limiting the model to African American recipients resulted in similar findings; African American recipients with 0 HLA-A, -B MMs had an estimated increase in PRA of 5%, and recipients with four HLA-AB MMs had an estimated increase in PRA of 24%. The adjusted odds ratio for becoming newly sensitized for African Americans was 2.4 (95% CI 1.7–3.5) associated with two HLA-A MMs relative to 0 HLA-A MMs, which was higher than in the general study population (AOR 2.0). Pediatric recipients had a higher average increase in PRA and the adjusted increase of HLA-A, -B mismatching was 12% for 0 mismatches and 31% for four mismatches. The relative likelihood of becoming newly sensitized was similar to that of the overall population. HLA-matching for HLA-A alone had a significant effect in reducing the probability of sensitization in the general population and in the subgroups described earlier.

Six month AR during the initial transplant was associated with significantly higher rates of new sensitization (AR=57%, No AR=48%, $P<0.001$). This association was consistent within HLA-mismatching groups, that is, AR rates were higher in patients with increased mismatching but also higher for newly sensitized patients by HLA mismatching (0 HLA-MM, 34% AR in newly sensitized patients and 24% AR in patients not newly sensitized [$P=0.07$]; 1–4 HLA-MM, 57% and 50%, respectively [$P<0.001$]; and five to six HLA-MM, 60% vs. 52%, respectively [$P=0.003$]). The proportion of patients who were newly sensitized (PRA>30) was relatively stable for relisted patients between 1995 and 2002 (ranging between 20% and 28%). However, beginning in 2003 through 2007, this proportion rose steadily 2003 (30%), 2004 (35%), 2005 (37%), and 2006 (45%).

DISCUSSION

HLA sensitization remains one of the most recalcitrant problems in kidney transplantation. A high PRA not only makes a second kidney transplant riskier but might make it outright impossible because of the difficulty of finding a crossmatch negative kidney (*17*). Our study demonstrates that HLA-matching, although conceivably an acceptable trade off between increased minority allocation and the impact on primary kidney transplant survival, has beyond that calculation a significant impact on sensitization of the recipient, which is problematic if the patient needs a second transplant. As HLA-matching has been de-emphasized progressively in the United States, the number of patients with a high PRA awaiting a second transplant is also increasing (*11*, *15*). In fact, for the population we analyzed, until 2003 only 20% to 28% of patients became newly sensitized by their first transplant, whereas now up to 45% of retransplant candidates are newly sensitized with a PRA more than 30%. This could certainly be due to other factors than decreased HLA matching

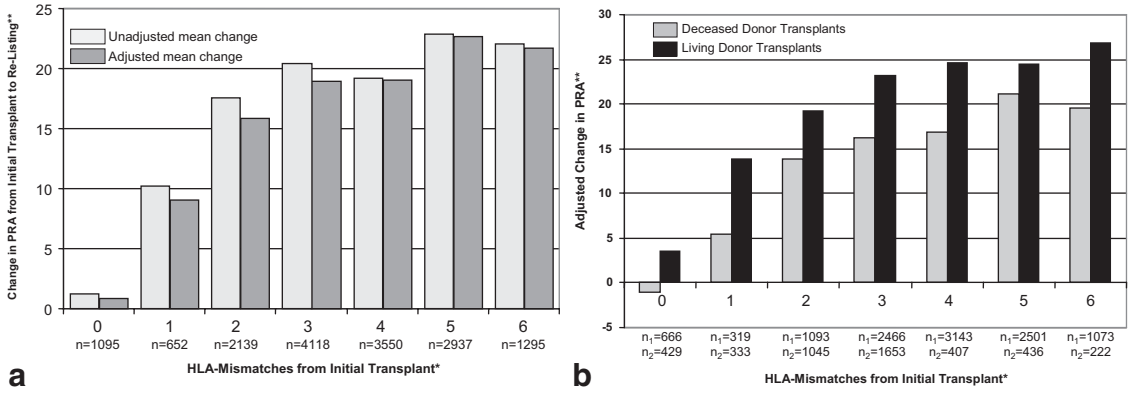

FIGURE 1. (a) Change in PRA% from Initial Transplant to Re-Listing by HLA-Mismatching from Initial Transplant. (b) Adjusted change in PRA% from Initial Transplant to Re-Listing by HLA-Mismatching from Initial Transplant comparing living to deceased donor transplants. *Total HLA-A/-B/-DR mismatches from initial transplant; n=194 patients excluded based on missing levels of one or more covariates; n_1 represents the number of deceased donor transplants in each HLA MM category, n_2 represents the number lf living donor transplants in each HLA MM category. **Adjusted change represent least squared mean estimates from general linear model adjusted for donor type, recipient and donor age, recipient and donor race, recipient and donor gender, primary diagnosis, body mass index, and time to relisting from initial transplant.

TABLE 3. Logistic model for likelihood of candidate's newly sensitized at relisting

Explanatory factor (reference group)	Level	Adjusted odds ratio	95% CI	*P*
Donor type (living donor)	Deceased Donor	1.11	0.98–1.26	0.09
Recipient age (18–34 yr)	0–11	1.28	0.99–1.66	<0.001
	12–17	1.09	0.89–1.33	
	35–54	0.79	0.70–0.89	
	55–64	0.73	0.60–0.89	
	65+	0.49	0.34–0.71	
Recipient race (white)	African American	1.26	1.11–1.44	<0.001
	Other	0.95	0.80–1.12	
Donor age (18–49 yr)	0–17	1.03	0.87–1.21	0.03
	50–59	0.82	0.71–0.95	
	60+	0.87	0.71–1.07	
Donor race (white)	African American	0.85	0.73–1.00	0.07
	Other	1.07	0.90–1.27	
Candidate gender (male)	Female	0.90	0.81–1.00	0.05
Months to relisting (0–24)	25–60	1.99	1.74–2.27	<0.001
	61–96	1.87	1.62–2.16	
	97+	2.05	1.76–2.38	
Diabetes as primary diagnosis (yes)	No	1.05	0.90–1.22	0.55
Candidate BMI (25–29)	Missing	1.14	0.98–1.32	0.40
	<20	1.09	0.90–1.33	
	20–24	1.00	0.87–1.16	
	30–34	0.97	0.80–1.18	
	35+	0.98	0.76–1.25	
Total HLA-A, -B, -DR mismatches (0)	1	2.60	1.92–3.52	<0.001
	2	2.94	2.32–3.73	
	3	3.14	2.52–3.93	
	4	3.04	2.41–3.82	
	5	3.50	2.77–4.43	
	6	3.84	2.91–5.06	

[a] Among patients nonsensitized at initial transplant (n=6685); sensitized defined as a PRA more than 0%.
CI, confidence interval; HLA, human leukocyte antigen; BMI, body mass index; PRA, panel reactive antiobody.

such as more sensitive technologies for measuring antibodies, but it reiterates the clinical magnitude of the problem. The UNOS organ allocation system has moved away from HLA matching mostly because of allocation logistics driven by the desire to equalize minority access to transplantation accepting the implication of possibly higher AR rates and lower graft survival. Other countries have preserved HLA matching as the primary driver for organ allocation. The minority problem is probably limited to the United States with European countries not facing similar requirements. Also geographical

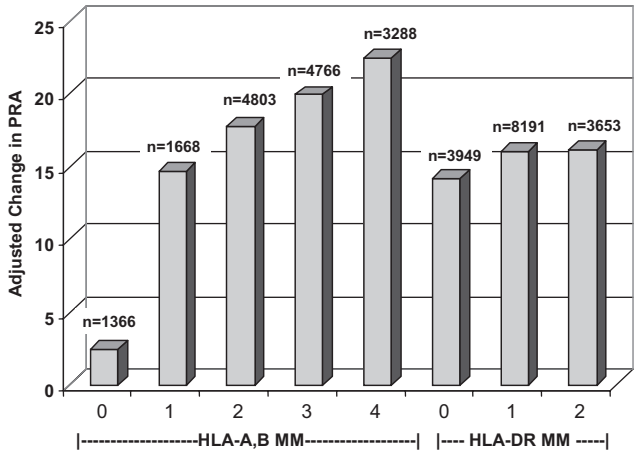

FIGURE 2. Independent effect of HLA-Mismatches on Adjusted Change in %PRA at Re-Listing. Model adjusted for all variables in primary model displayed in Table 2; however, HLA-A and -B are combined in this model, and HLA-DR is separate. *Bars* represent the independent effect of HLA-matching on change in PRA at relisting. HLA, human leukocyte antigen; PRA, panel reactive antibody.

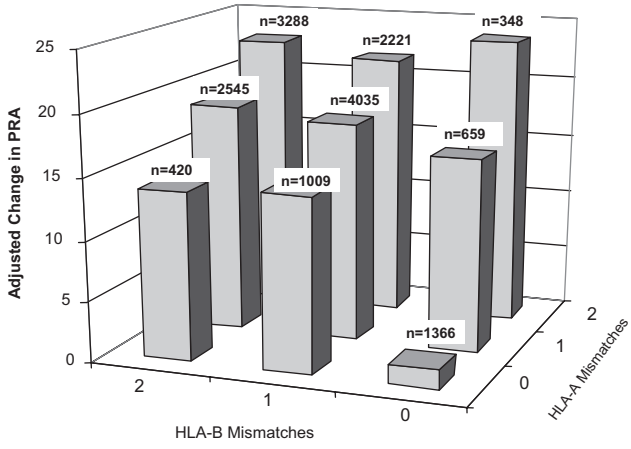

FIGURE 3. Adjusted Mean Change in (PRA)% from Initial Transplant to Re-Listing by Interaction of HLA-A and HLA-B Mismatching. Adjusted change represent least squared mean estimates from general linear model adjusted for donor type, recipient and donor age, recipient and donor race, recipient and donor gender, primary diagnosis, and body mass index. HLA-DR mismatching and time to relisting from initial transplant.

distances vary between allocation systems and the competing risk factors of cold ischemia time and HLA matching might weigh differently in small versus large organ allocation areas (*9*). Even though it is difficult to compare data from different countries, it is clear that the United States is facing a more significant problem with sensitized patients listed for a second transplant than Europe and other countries. As other countries have held on to their HLA matching policies for organ allocation, while the United States has moved away from it, this certainly could be seen as secondary evidence that HLA matching matters also for the risk of getting sensitized. This is certainly an important problem as graft survival is significantly lower in patients with a high PRA, and much of the poorer graft survival in the retransplant population can in part be explained by the higher PRA (*11*, *14*). More importantly, patients with a high PRA have a significantly longer waiting time for transplantation, and a substantial proportion will never get transplanted because of their high sensitization. The longer waiting time translates into a greater likelihood of dying and worse outcomes for those transplanted (*18*). Therefore, if better HLA matching indeed prevents sensitization in a significant proportion of patients in need for a second transplant, it was probably a smart move by the countries that were able to hold on to HLA matching as an important driver organ allocation.

A previous report of 449 patients transplanted before the cyclosporine era suggested that poor HLA match led to higher sensitization after graft failure and might lead to lower rate of retransplantation (*19*). This small report though, did not stop the progressive de-emphasis in matching that occurred subsequently probably in part driven by the thought that this might not be a problem with more efficacious immunosuppression in the calcineurin inhibitor era. A more recent study of 149 transplant patients suggested also a high correlation between degree of matching and specific allosensitization in patients who had rejected their transplant (*20*). Contrariwise a recent publication investigating pediatric kidney allocation models found no effect of HLA mismatching on sensitization defined by a PRA more than 30% (*21*).

Our results show that even with modern immunosuppression, a staggering 50% of patients became newly sensitized after their first transplant, and this appeared to be strongly driven by increasing HLA MMs, 34% of them becoming highly sensitized after their first transplant. Of clinical relevance, only 10% of patients with an A-, B-matched kidneys who were unsensitized at the time of their first transplant became newly sensitized when they needed to be relisted after graft loss.

Another striking finding was that among 1095 patients who received a 0-A, B, DR antigen-mismatched kidney transplant that were subsequently relisted after graft loss for a second transplant, there was minimal or no increase in panel antibody reactivity in both the univariate and the multivariate models. By contrast, there was a significant increase in PRA by increasing HLA MM (Fig. 1a). Figure 1(a) also shows that the adjusted rates are somewhat different from the unadjusted rates of sensitization. This is because subgroups of patients have a higher risk for sensitization, such as African American patients, younger patients. Interestingly, also recipients of a younger donor kidney had a higher risk for sensitization (Table 2). The same risk factors are present for being newly sensitized, which is probably clinically the more important metrics because these are patients who did not have anti-HLA antibodies at the time of their first transplant but were newly sensitized at time of listing. African American recipients, younger patients, and again recipients of younger organs were more likely to get newly sensitized but again as emphazised by the magnitude of the odds ratios the most significant risk factor was a higher HLA MM at the time of the first transplant (Table 3). This trend was similar in deceased donor compared with living donor transplants (Fig. 1b), even though living donor transplants seemed to have overall a higher risk for increased sensitization (Table 2).

This effect seems to be primarily associated with HLA-A and -B MMs, as shown in Figure 2. The PRA is a measure of class I HLA sensitization, but current technology allows the characterization of class II antibodies with equal accuracy. Although class II antibodies can cause hyperacute rejection, this occurs at high antibody levels, and in general, multiple reports suggest that class II antibodies are not as harmful as class I antibodies (*22*). This certainly applies similarly to the risk of sensitization as this study suggests.

In fact, from a practical standpoint, trying to match for A, B rather than A, B, DR can be applied to more patients. In this regard, we made the additional observation that matching only for HLA-A is associated with a lower PRA at relisting and a lower number of newly sensitized patients This can be explained by the fact that the frequency of some HLA-A antigens is higher than that of HLA-B antigens (e.g., antibodies reacting with the two most frequent A antigens in whites, A1 and A2, give a PRA of approximately 63% based on their frequency; the PRA given by antibodies to the most frequent B antigens, B7 and B44, would be 42%) (*23*). Clearly, although matching for both HLA-A and -B could have the greatest impact on preventing sensitization, DR matching seems to play a marginal role.

This data also possibly redefine the importance of HLA matching in the selection of living donor candidates when multiple donors are available should be reconsidered. Currently, insurance policies often only pay to work up one potential donor at a time, whereas it might be advisable to test all potential donors and work up first the one best matched to minimize the risk for sensitization.

Hypothetically new matching strategies based on these results could conceivably reduce the risk of sensitization, especially if coupled with other means such as minimization of blood transfusions after graft loss. Another hypothesis to explore is whether transplant nephrectomies before tapering off the immunosuppression after graft loss can prevent allosensitization in patients returning to dialysis who are not yet sensitized.

The average survival of a kidney transplant is 8 years for deceased and 12 years for living donor transplants (*1*), and therefore younger patients have a higher likelihood of needing more than one kidney transplant during their lifetime (*24*). Considering the data from our study, one could make the case that in younger patients with a likelihood of needing a second transplant in the future HLA matching should be a important criteria for selecting their initial transplant kidney. Younger patients have a higher chance to become sensitized by a first failed transplant (Table 2), and they have a similar risk increase with increasing HLA-MM as the general population, in addition to a higher likelihood based on their life expectancy to need multiple transplants throughout their lifetime.

Preventing sensitization might be a more efficient approach than treating it, as patients sensitized by their first transplant need to rely on costly and inconsistent desensitization protocols that allow for less successful repeat transplants (*17*).

The de-emphasis of HLA matching is projected to continue in the development of future allocation systems currently under development by UNOS's KARS committee, which is based on life years gained from transplant (*25*). There are important logistic reasons to try to minimize HLA matching in the kidney allocation system, but the calculations of the potential downsides have always focused on the first transplant episode. In the design of a new allocation system, rather than just focusing on the single transplant episode, a lifetime view for patients with end-stage renal disease should be considered. We need to consider carefully the possibility of the need for multiple kidney transplants in the future and the problems, which may ensue from sensitization stimulated by a first mismatched transplant. Our data also suggest that matching can perhaps be simplified by considering fewer alleles (A, B, or A alone) and possibly restricted to selected populations with long projected life expectancy.

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