Effect of Changing the Priority for HLA Matching on the Rates and Outcomes of Kidney Transplantation in Minority Groups

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Abstract

Background

HLA typing and the time a patient has spent on the waiting list are the primary criteria used to allocate cadaveric kidneys for transplantation in the United States. Candidates with no HLA-A, B, and DR mismatches are given top priority, followed by candidates with the fewest mismatches at the HLA-B and DR loci; this policy contributes to a higher transplantation rate among whites than nonwhites. We hypothesized that changing this allocation policy would affect graft survival and the racial balance among transplant recipients.

Methods

We estimated the relative rates of kidney transplantation according to race resulting from the current allocation policy and racial differences in HLA antigen profiles, using a Cox model for the time from placement on the waiting list to transplantation. Another model, also adjusted for HLA-B and DR antigen profiles, estimated the relative rates of kidney transplantation that would result if the distribution of these antigen profiles were identical among the racial and ethnic groups. We also investigated the effect of HLA matching on the risk of graft failure, using a Cox model for the time from the first transplantation to graft failure. The results of the two analyses were used to estimate the change in the racial balance of transplantation and graft-failure rates that would result from the elimination of HLA-B matching or HLA-B and DR matching as a means of assigning priority.

Results

Eliminating the HLA-B matching as a priority while maintaining HLA-DR matching as a priority would decrease the number of transplantations among whites by 4.0 percent (166 fewer transplantations over a one-year period), whereas it would increase the number among nonwhites by 6.3 percent and increase the rate of graft loss by 2.0 percent.

Conclusions

Removing HLA-B matching as a priority for the allocation of cadaveric kidneys could reduce the existing racial imbalance by increasing the number of transplantations among nonwhites, with only a small increase in the rate of graft loss.
The matching of histocompatibility antigens between donors and recipients improves the outcomes of kidney transplantation. Matching provides the greatest advantage when the donor and the recipient have no antigens mismatched or when matching is identical at all six HLA loci. However, lesser degrees of matching still offer some advantage. The current allocation policy for cadaveric kidneys in the United States gives priority to candidates who have no mismatches at any of the loci (zero mismatches) on a national basis and candidates who have zero, one, or two mismatches at the HLA-B and DR loci on a local, regional, and then national basis.

Because of racial or ethnic differences in the frequency of alleles at each locus, whites are more likely than those in other racial or ethnic groups to find a good match in the donor kidney pool. This biologic fact, when coupled with the current allocation policy, increases the transplantation rate among white candidates while it conversely reduces the access of candidates with less common HLA phenotypes, including those who are members of minority groups. These effects contribute substantially to the twofold higher rate of transplantation among white candidates, as compared with candidates who are members of minority groups. 

We examined the possible effect of two potential changes to the current policy of organ allocation: eliminating the priority assigned to matching of HLA-B and DR loci and eliminating the priority for HLA-B matching while retaining the priority for HLA-DR matching. We evaluated the estimated effects of these policy changes on national outcomes, including the racial and ethnic mix of transplant recipients and graft survival after kidney transplantation, as well as their effects on transplants involving at least one mismatch, while maintaining the priority assigned to transplantation of kidneys with zero mismatches.

Methods

Source of Data
We used national data on transplantation rates and graft survival from the Scientific Registry of Transplant Recipients. This registry includes data collected by the Organ Procurement and Transplantation Network, the Centers for Medicare and Medicaid Services for patients with end-stage renal disease, and the Social Security Death Master File.

Patients were excluded from all analyses if they were on a waiting list for or had received a multiorgan transplant or if they were missing information about the HLA-A, B, or DR loci. We modeled transplantation rates for patients added to the waiting list between January 1, 1994, and December 31, 1997, beginning on the first day of placement on the list. The patients’ characteristics were assessed at the time they were placed on the list. Patients were excluded if they had missing information on age, racial or ethnic group, or date of placement on the waiting list; less than 1 percent of patients were excluded for these reasons. After exclusions, the study sample numbered 71,595 candidates on the waiting list. Follow-up ended on June 30, 2001.

Graft survival was modeled for patients who received a first cadaveric kidney transplant with at least one HLA mismatch between March 6, 1995, and June 30, 2001; follow-up was continued until December 31, 2001. The characteristics of the donors and recipients were recorded at the time of transplantation. Graft failure was defined as a record of graft failure, death, or need to resume long-term dialysis. We ascertained a patient’s death by finding a record of the death in any of the data sources. Fifteen percent of recipients were excluded because information on the donor’s age, creatinine level, or mismatch score was missing. After exclusions, the study sample included in the analysis of graft-failure rates numbered 32,609 transplant recipients.

Statistical Analysis
All statistical analyses were performed with the use of SAS software, version 8.2. We determined the relative rates of transplantation of cadaveric kidneys with at least one HLA mismatch from the time of placement on the waiting list according to the racial or ethnic group, using Cox proportional-hazards regression; data were censored if transplantation involved zero mismatches or a living donor or at the time of death, removal from the waiting list, or the end of the study, whichever came first. The transplantation models were adjusted for the following characteristics of the candidates: age, sex, blood type, race, ethnic group, year of placement on the waiting list, cause of end-stage renal disease, panel-reactive antibody levels at the time of placement on the waiting list, type of dialysis, presence or absence of blood transfusions before placement on the waiting list, presence or absence of previous transplantation, and source of payment.

Three analyses were carried out. The first analysis used the current system of allocation (without
adjustment for the candidates’ HLA-B or DR antigen profile). The second analysis eliminated only the priority assigned to HLA-B matching (with adjustment for the candidates’ HLA-B antigen profile, so that distribution of HLA-B antigens was consistent among the racial and ethnic groups), and the third analysis eliminated the priority assigned to both HLA-B and DR matching (with adjustment for the candidates’ HLA-B and DR antigen profile, so that the distribution of HLA-B and DR antigens was consistent among the racial and ethnic groups).

We used adjusted relative rates of transplantation among racial groups to estimate the residual differences due to race, after differences in HLA antigens were accounted for, to approximate the relative rate of transplantation that would result if matching of HLA-B alone or of both HLA-B and DR were not used in the allocation system among candidates with at least one HLA mismatch.

To evaluate the effect on access to transplantation of removing points scored for HLA-B or HLA-B and DR matching, we calculated the percent change in transplantation rates for each racial or ethnic group, on the basis of the above estimates. The percent change in transplantation rate was determined for each racial or ethnic group by calculating the difference between the HLA-adjusted relative rate of transplantation (eliminating the priority for HLA-B matching alone [second analysis] or both HLA-B and DR matching [third analysis]) and the non–HLA-adjusted relative rate of transplantation (the current allocation system [first analysis]), divided by the non–HLA-adjusted relative rate. This ratio was then multiplied by a correction factor to account for the fact that the number of available kidneys is fixed; thus, an increase in the number of transplantations among nonwhites is, by definition, a decrease in the number among whites: \( 1 ÷ (1 + \text{adjusted relative risk} \times C) \), where \( C \) is the ratio of the number of white candidates to the number of nonwhite candidates. The percent change was then multiplied by the actual number of cadaveric organs with at least one HLA mismatch that was transplanted in each racial or ethnic group in order to determine the number of organs that would have been transplanted in a year (referenced to 2000), if HLA-B or HLA-B and DR matching had not been used in the allocation process.

In an alternative calculation, we compared the actual number of organs transplanted with the number predicted if all candidates had had identical (average) HLA antigens. This calculation used the expected number of transplantations for each patient, on the basis of predictions from a Cox model, adjusted for all previously listed variables pertaining to the candidates, plus the distribution of HLA-B and DR antigens, which was changed to reflect the average mixture of HLA antigens for the entire study group. This calculation provides a plausible approximation of the allocation of donor kidneys that would result from the elimination of the priority for HLA matching. The average HLA-B antigen profile was then substituted to approximate the effect of removing HLA-B matching as a priority, and the average HLA-B and DR profile was then substituted to approximate the removal of HLA-B and DR matching as a priority. A new expected number of transplantations for each scenario was calculated by adding up the number of candidates in each racial or ethnic group.

The effect of HLA mismatching on the time from first transplantation to graft failure for recipients of a graft with at least one mismatch was also investigated with the use of Cox models. The relative risks of graft failure among patients with one mismatch and patients with two mismatches, as compared with patients with zero mismatches, at the HLA-A, B, and DR loci were estimated with adjustment for the following donor variables: age at death, sex, race, ethnic group, year of donation, presence or absence of a history of hypertension, presence or absence of impaired renal function (as defined by a final serum creatinine level of more than 1.5 mg per deciliter [133 µmol per liter]), and presence or absence of cerebrovascular accident as the cause of death. The models were also adjusted for the recipient’s age at transplantation, sex, race, ethnic group, body-mass index, cause of end-stage renal disease, duration of therapy for end-stage renal disease, presence or absence of blood transfusions before transplantation, the number of HLA mismatches, panel-reactive antibody level, and duration of cold ischemia.

We approximated the number of mismatches that would result at the HLA-B and DR loci if HLA-B and DR matching was eliminated as a priority by randomly assigning organs to candidates within each blood group and calculating the resulting number of mismatches for each potential recipient. We then used the relative risks of failure on the basis of the number of mismatches resulting from random allocation to calculate a new expected number of graft failures for each scenario. We computed the total number of potential failures with the use of
random matching by summing the new expected numbers among all recipients.

In a sensitivity analysis, we restricted the allocation of organs according to blood type and organ-procurement organization. The effect of defining death as graft failure was also examined. The rates of death and rejection episodes within the first six months after transplantation were analyzed in a similar manner in other sensitivity analyses.

RESULTS

Tables 1 and 2 show the demographic makeup of the study populations. Table 1 summarizes the racial and ethnic characteristics of the candidates who were added to the waiting list during the study period. Whites made up 65.4 percent of those listed; blacks, 28.1 percent; Asians, 4.6 percent; and other racial groups, 1.9 percent. A total of 11.5 percent of the population was Hispanic, and 88.5 percent was non-Hispanic. The racial and ethnic distribution of recipients of a cadaveric transplant with at least one mismatch was similar to that of candidates on the waiting list. Zero, one, or two HLA-B or DR mismatches occurred in 58.8 percent of recipients with at least one mismatch of any type; in this subgroup, whites received 67.9 percent of these kidneys, as compared with 64.1 percent in the overall group that received kidneys with at least one mismatch (Table 2).

Table 3 shows the actual number of transplantations according to race in 2000 and the predicted change in the number that would have occurred with the elimination of matching for HLA-B alone or HLA-B and DR as a priority. Elimination of the priority for matching at both loci would have provided the greatest increase in the number of transplantations performed in nonwhites, shifting 214 (5.2 percent) from whites to nonwhites in 2000. Elimination of the priority for matching at the HLA-B locus alone would have shifted 166 transplantations (4.0 percent) to nonwhites. Thus, elimination of the priority for matching at the HLA-B locus alone accounts for 77.6 percent (166 of 214) of the predicted increase in transplantations among nonwhites, shifting 214 (5.2 percent) from whites to nonwhites in 2000. Elimination of the priority for matching at the HLA-B locus alone accounts for 77.6 percent (166 of 214) of the predicted increase in transplantations among nonwhites associated with the elimination of the priority for matching at both loci. An additional calculation according to ethnic group shows that fewer than 1.0 percent (0.7 percent in the absence of a priority for matching at HLA-B loci and 0.6 percent in the absence of a priority for matching at both HLA-B and DR loci) of the organs would have been shifted from non-Hispanic to Hispanic recipients (Table 3).

Figure 1 shows the projected improvement in the transplantation rates for each race, as compared with whites. The deficit would have been reduced by eliminating the allocation priority for either HLA-B matching alone or both HLA-B and DR matching. The model predicts that eliminating the priority for HLA-B matching while maintaining the priority for HLA-DR matching would account for most of the deficit among nonwhites.

The effect of matching at the HLA-A, B, and DR loci on the relative risks of graft loss is shown in Figure 2. The effect of increasing the number of mismatches at each locus is compared with the effect of having no mismatches at each locus, after adjustment for the effects of the other two loci. Having one or two mismatches at the HLA-A or B locus, as compared with zero mismatches, had no statistically significant effect after adjustment for mismatches at

<table>
<thead>
<tr>
<th>Race or Ethnic Group</th>
<th>Waiting-List Population (N=71,595)</th>
<th>0, 1, or 2 HLA-B or DR Mismatches (N=19,163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>20,105 (28.1)</td>
<td>5,169 (27.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>3,300 (4.6)</td>
<td>555 (2.9)</td>
</tr>
<tr>
<td>Other</td>
<td>1,382 (1.9)</td>
<td>429 (2.2)</td>
</tr>
<tr>
<td>White</td>
<td>46,808 (65.4)</td>
<td>13,010 (67.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8,232 (11.5)</td>
<td>2,134 (11.1)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>63,363 (88.5)</td>
<td>17,029 (88.9)</td>
</tr>
</tbody>
</table>

* The interval studied differs from that in Table 1 (1994 to 1997) so as to reflect the typical amount of time spent waiting for a kidney transplant.

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<table>
<thead>
<tr>
<th>Race or Ethnic Group</th>
<th>Waiting-List Population (N=71,595)</th>
<th>0, 1, or 2 HLA-B or DR Mismatches (N=19,163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>9,544 (29.3)</td>
<td>5,169 (27.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>1,350 (4.1)</td>
<td>555 (2.9)</td>
</tr>
<tr>
<td>Other</td>
<td>823 (2.5)</td>
<td>429 (2.2)</td>
</tr>
<tr>
<td>White</td>
<td>20,892 (64.1)</td>
<td>13,010 (67.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3,913 (12.0)</td>
<td>2,134 (11.1)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>28,696 (88.0)</td>
<td>17,029 (88.9)</td>
</tr>
</tbody>
</table>

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Table 2. Racial and Ethnic Characteristics of Recipients of a Cadaveric Kidney with at Least One HLA Mismatch, 1995–2001.*

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* The interval studied differs from that in Table 1 (1994 to 1997) so as to reflect the typical amount of time spent waiting for a kidney transplant.
the other two loci (P values ranged from 0.24 to 0.43). In contrast, having one or two mismatches at the HLA-DR locus, as compared with zero mismatches, did increase the risk of graft failure (relative risk with one mismatch, 1.15; P<0.001; relative risk with two mismatches, 1.26; P<0.001). These results suggest that eliminating HLA-DR matching as a priority would have a greater negative effect on graft survival than would eliminating HLA-B matching as a priority.

Table 4 lists the actual numbers of graft failures in 2000 according to racial and ethnic group for transplantations performed between March 6, 1995, and June 30, 2001, and shows the predicted effect of the two alternative allocation strategies. Elimination of HLA-B and DR matching as a priority would have significantly increased the risk of graft loss (relative risk, 1.08; P<0.001), as compared with keeping the current allocation policy. Elimination of HLA-B matching as a priority while maintaining HLA-DR matching as a priority would have resulted in a substantially smaller increase in the relative risk (relative risk, 1.02; P<0.001).

We conducted alternative calculations and sensitivity analyses to evaluate the stability of these results. Alternative calculations of the effect of eliminating HLA-B or HLA-B and DR matching as a priority yielded results that were very similar to those already shown. Randomly matching donors and candidates within an organ-procurement organization and a blood type and counting deaths as graft failures resulted in only small changes (less than 1.0 percent) in the relative risk of graft loss. In an analysis of death rates, the estimated increase in the risk of death was not significantly elevated by the removal of HLA-B matching as a priority (relative risk as compared with keeping the current allocation policy, 1.01; P=0.11); however, the estimated risk of

### Table 3. Actual Number of Transplantations Performed in 2000 and Number Expected if Matching for HLA-B Alone or HLA-B and DR Was No Longer a Priority.

<table>
<thead>
<tr>
<th>Race or Ethnic Group</th>
<th>No. of Transplantationsa</th>
<th>Change Resulting from Elimination of HLA-B Matching</th>
<th>Change Resulting from Elimination of HLA-B and DR Matching</th>
<th>Percentage of Effect Accounted for by the Elimination of HLA-B Matching vs. the Elimination of HLA-B and DR Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>2154</td>
<td>+138 (+6.4)</td>
<td>+173 (+8.0)</td>
<td>79.8</td>
</tr>
<tr>
<td>Asian</td>
<td>354</td>
<td>+21 (+5.9)</td>
<td>+29 (+8.2)</td>
<td>72.4</td>
</tr>
<tr>
<td>Other</td>
<td>132</td>
<td>+7 (+5.3)</td>
<td>+12 (+9.1)</td>
<td>58.3</td>
</tr>
<tr>
<td>White</td>
<td>4120</td>
<td>-166 (-4.0)</td>
<td>-214 (-5.2)</td>
<td>77.6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>824</td>
<td>+35 (+4.2)</td>
<td>+38 (+4.6)</td>
<td>92.1</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>5799</td>
<td>-35 (-0.6)</td>
<td>-38 (-0.66)</td>
<td>92.1</td>
</tr>
</tbody>
</table>

a Actual numbers of transplantations involving at least one HLA mismatch were estimated on the basis of the total number of transplantations listed in the 2001 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients and percentages of zero-mismatch transplantations according to race.
death was 7 percent higher with the removal of both HLA-B and DR matching as a priority (relative risk, 1.07; P<0.001). Similarly, removal of HLA-B and DR matching as a priority increased the estimated risk of rejection by 5 percent within the first six months (P<0.001), whereas removal of HLA-B matching as a priority had no significant effect (P=0.78).

**DISCUSSION**

Our results demonstrate the inherent conflict between the utility and equity of HLA-based allocation of kidneys for transplantation. This tension arises from the dual effect of HLA matching: it improves the outcome of transplantation (utility) but decreases the number of nonwhites who undergo transplantation (equity). Table 3 clearly shows the shift in the number of transplantations from whites to nonwhites as the priority for matching in the allocation system among organs with at least one mismatch is changed from the current system, which gives priority to matching donor and recipient at both the HLA-B and the HLA-DR loci, to one that emphasizes matching at the HLA-DR locus alone or to a system with no priority for matching. This shift is seen because whites are more likely than persons of other races to be matched to a donor with the use of the current allocation system; closer matches are given priority, causing whites to receive transplants more frequently. Our findings suggest that the HLA-related racial and ethnic disparity would be decreased by eliminating the matching at the HLA-B locus as a priority.

Better HLA matching improves the outcomes of kidney transplantation.2,3 Our estimates, based on a very large sample, demonstrate that in the current era, matching at the HLA-B locus has only a minor and nonsignificant effect on graft outcome. By contrast, our results also confirm that better matching at the HLA-DR locus results in a significant improvement in graft outcome.

Because of the improvement in graft survival that accompanies the use of HLA-DR matching as a priority, decreasing the number of well-matched kidneys transplanted would be expected to increase the rate of graft failure. We found that the rate of graft loss was greatest when HLA-DR matching was eliminated as a priority and was closest to the actual rate of graft failure in 2000 when HLA-B matching alone was eliminated as a priority. In practice, removal of HLA-B matching as a priority is unlikely to result in completely random matching at the HLA-B locus, because negative cross-matching is also likely to lead indirectly to residual HLA matching. Thus, we believe that our results overestimate the adverse effects of removing HLA-B matching as a priority.

**Figure 2. Relative Risk of Graft Failure with One or Two Mismatches at Each HLA Locus as Compared with Zero Mismatches.**

The analysis of each HLA locus has been adjusted for the effects of the other two loci. The relative risks have been adjusted for the following donor variables: age at death, sex, race, ethnic group, year of donation, presence or absence of a history of hypertension, presence or absence of impaired renal function (defined by a final serum creatinine level of more than 1.5 mg per deciliter [133 µmol per liter]), and presence or absence of cerebrovascular accident as the cause of death — and the following recipient variables: age at transplantation, sex, race, ethnic group, body-mass index, cause of end-stage renal disease, duration of therapy for end-stage renal disease, presence or absence of blood transfusions before transplantation, number of HLA mismatches, panel-reactive antibody level, and duration of cold ischemia. The grafts with zero mismatches served as the reference category.
Similarly, our analysis may overstate the magnitude of the shift in organs from whites to minority groups. We expect the latter effect to be somewhat smaller because we did not include positive cross-matches. This potential limitation, however, should not affect the wisdom of a policy change regarding HLA-B matching. The actual degree to which this change will reduce the disadvantage among patients in minority groups who are on the waiting list can only be determined in future studies conducted after the elimination of this policy.

Our results suggest that modifying the policies regarding kidney allocation to eliminate the priority given to matching at the HLA-B locus would have little adverse effect in terms of graft loss. Such a change would reduce the tension inherent in the current allocation policy by improving equity without sacrificing utility. Specifically, this change would lead to an increase in the number of nonwhites who receive a transplant without a significant increase in the number of organs lost. Since, as compared with dialysis, transplantation increases survival in all racial and ethnic groups, allocation policies that unnecessarily restrict access to transplantation should be avoided.

Table 4. Actual Number of Graft Failures in 2000 and Number Expected if Matching for HLA-B Alone or HLA-B and DR Was No Longer a Priority.

<table>
<thead>
<tr>
<th>Race</th>
<th>Actual No. of Graft Failures</th>
<th>Change Resulting from Elimination of HLA-B Matching</th>
<th>Change Resulting from Elimination of HLA-B and DR Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1779</td>
<td>+36</td>
<td>+142</td>
</tr>
<tr>
<td>White</td>
<td>1057</td>
<td>+21</td>
<td>+85</td>
</tr>
<tr>
<td>Black</td>
<td>631</td>
<td>+13</td>
<td>+51</td>
</tr>
<tr>
<td>Other</td>
<td>91</td>
<td>+2</td>
<td>+7</td>
</tr>
</tbody>
</table>

* Calculations are based on random matching of donors and recipients with compatible blood types. The rates are for graft failures occurring in 2000 after transplantation between March 6, 1995, and June 30, 2001. The average duration of follow-up was 2.7 years. One- and three-year rates of graft survival for the entire group were 87.2 percent and 77.1 percent, respectively. The relative risk of graft failure was 1.02 (P<0.001) with the elimination of HLA-B matching as a priority and 1.08 (P<0.001) with the elimination of HLA-B and DR matching as a priority, as compared with keeping the current allocation policy.

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REFERENCES


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