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# Influence of HLA and CREG Matching in African-American Primary Cadaver Kidney Recipients: UNOS 1991–1995

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THERE have been only limited investigations on the influence of HLA match on organ transplant outcome in African-Americans.[1,2] To obtain this information, a multivariate analysis was performed of 31,291 cases of primary cadaver kidney transplantation reported to the UNOS Scientific Registry between 1991 and 1995.[3] The collection included 8111 African-Americans, for whom follow-up was to January 1, 1997. The study involved a triple university collaboration involving experts in clinical transplantation, histocompatibility, and biostatistical methodology.

## HLA MATCHING

The Pittsburgh experience was excluded from the UNOS analysis and reported separately[3] because tacrolimus was routinely given during the period of case accrual. Nevertheless, 3.2% of the UNOS patients at other centers were treated with tacrolimus: 2.5% of the 8111 African-Americans and 3.4% of the 23,180 "all others."

In the total collection of 31,291 cases, 1-year graft survival with a zero mismatch was 89%. This fell by 3% to 86% with a single mismatch at either the A, B, or DR locus. Within the full range of one to six mismatches, 4% more were lost. As reported in detail elsewhere,[3] the small graft survival differences were statistically significant.

But how significant were these survival differences clinically? Part of the answer came from the distribution profile (Table 1). Only 174 (or 2.1%) of the 8111 African-Americans received a zero-mismatched kidney, compared to 9.9% in the 23,180 "all-other" population. At the other end of the matching scale, an additional 558 African-Americans (or 6.9%) received a six antigen (full-house) mismatch. Thus, 91.2% of the African-American recipients were in the one to five mismatch spectrum, which also bracketed more than 85% of the "all other" cases (Table 1).

The graft survival in African-Americans at the 1-year posttransplant milestone was not markedly lower than that of the "all other" population at any of the HLA mismatch levels. More relevant to the primary objective of our study, the degree of HLA mismatch had very little effect on 1-year African-American outcome. One-year allograft survival from the top to bottom of the one to five HLA mismatch range varied by less than 2% (Table 2). The lack of a stepwise effect also was evident in the one to five mismatch range of the "all other" population, where the 1-year survival did not vary by as much as 3% (Table 2).

By 3 years, graft survival in African-Americans had become inferior to the "all others" (Table 2). However, because survival declined by approximately 10% at every level of HLA compatibility, including zero mismatches, the difference in 3-year graft survival from one to five mismatches was only 2.4%, with a survival crossover of four

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**Table 1. Distribution of HLA Mismatches**

| African-Americans | HLA mismatches | All Others |
|---|---|---|
| 174 (2.1%) | 0 | 2286 (9.9%) |
| 206 (2.5%) | 1 | 1128 (4.9%) |
| 783 (9.7%) | 2 | 3225 (13.9%) |
| 2037 (25.1%) | 3 | 6034 (26.0%) |
| 2665 (32.9%) | 4 | 5877 (25.3%) |
| 1688 (20.8%) | 5 | 3509 (15.1%) |
| Subtotal 9 1.2% | | Subtotal 85.3% |
| 558 (6.9%) | 6 | 1211 (4.8%) |

**Table 2. % Graft Survival at 1 and 3 Years**

| African-Americans N = 8111 | HLA mismatches | All Others N = 23180 |
|---|---|---|
| 87.1 (73.4) | 0 | 89.2 (82.3) |
| 84.6 (68.7) | 1 | 86.9 (78.7) |
| 84.3 (68.2) | 2 | 86.4 (77.9) |
| 83.9 (67.5) | 3 | 86.2 (77.6) |
| 83.0 (65.9) | 4 | 84.5 (75.0) |
| 83.3 (66.3) | 5 | 84.0 (74.3) |
| Subtotal 91.2% | | Subtotal 85.3% |
| 81.5 (63.2) | 6 | 83.0 (72.9) |



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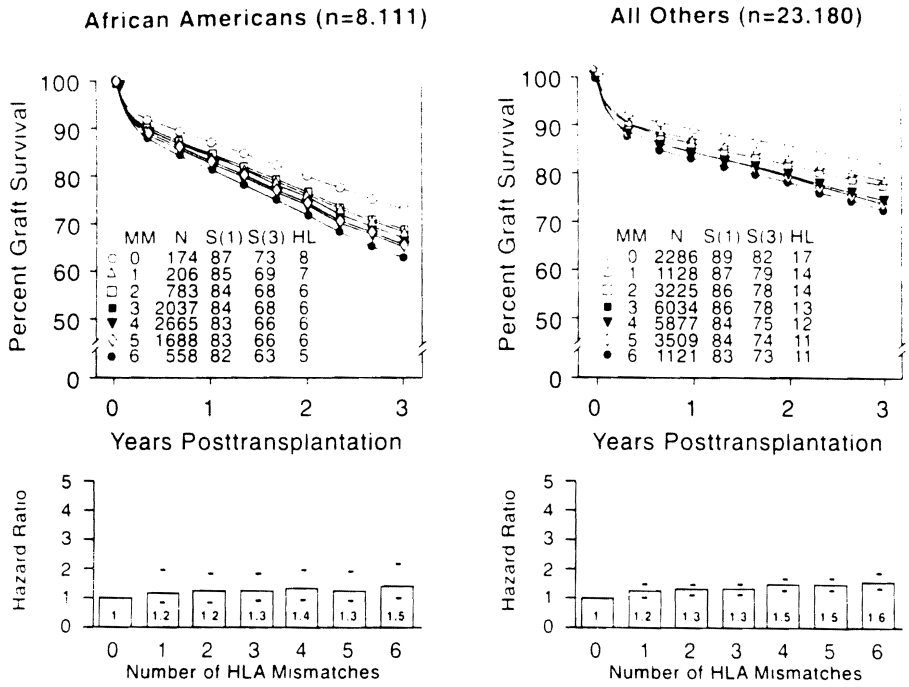


**Fig 1.** Graft survival and calculations of hazard ratios (relative risk) over the first 3 post-transplant years, based on number of HLA mismatches. The reference was provided by zero mismatch cases. HL = half life.

and five HLA mismatched tiers. The pattern of results in the "all other" recipient population (Table 2) was essentially the same.

An HLA-associated survival divergence between 1 and 3 years within the African-American population was obvious only with the stepdown from zero to the first mismatch, although there was a small effect from the fifth to the sixth mismatch. At all levels of HLA mismatch, however, the principal and relative separation of curves had already occurred by the end of the first year (Table 2). Although the percentages were slightly different in the 23,180 "all other" cases, the overall picture was much the same.

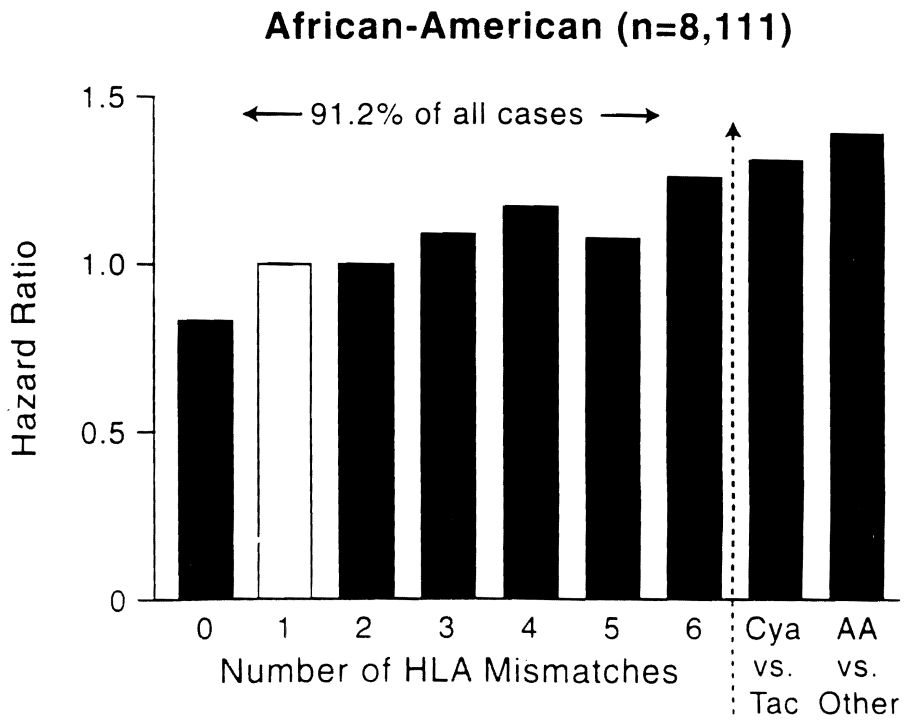


**Fig 2.** Relative risks of graft failure in African-Americans based on cumulative HLA mismatches, using one HLA mismatch population for the reference (hazard ratio = 1.0). The HR for cyclosporine was calculated with tacrolimus as reference. The HR for African-American status was calculated using "all others" as reference (1.0).

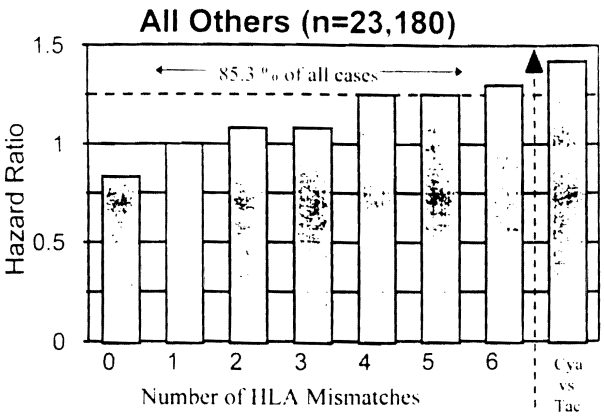


**Fig 3.** Relative risks of graft failure in "all other" than African-American recipients based on cumulative HLA mismatches using one HLA mismatch population as the reference (1.0). The reference hazard ratio for cyclosporine was provided by tacrolimus.

In Figure 1, the hazard ratio (or relative risk) over the first 3 years with various degrees of mismatch in African-Americans (left) or in all others (right), was calculated using the zero HLA mismatch as the reference standard of 1.0. The principal adverse effect came with the first mismatch, which for the African-Americans increased the relative risk of graft loss within 3 years to a modest 1.2. However, the relative risk only increased further to 1.3 from one to five mismatches. For the "all other" population (Fig 1, right), the relative risk between one and five mismatches rose from 1.2 to 1.5.

It has been known for more than 25 years that the absence of an HLA incompatibility (zero mismatch or six antigen mismatch) confers a graft survival advantage.[4,5] The practical question is what is the effect of various levels of mismatch. Consequently, the relative risk of cumulative mismatches was recalculated using the one HLA mismatch as the reference standard of 1.0. The relative risk for both African-American and the "all other" patients with a zero mismatch was then 0.83 (Figs 2 and 3). The relative risk in the spectrum of one to five mismatches that encompassed 91.2% of all African-American recipients increased only from 1.0 to 1.08 (Fig 2). This was less than the condition per se of being African-American versus "all other" (relative risk 1.38 using "all others" as the reference of 1.0), and it was less than the risk of treating with cyclosporine (1.31) rather than with tacrolimus (1.0) (Fig 2).

In the "all other" population (Fig 3), the relative risk rose only from the reference of 1.0 provided by the single HLA mismatch to 1.25 with five mismatches. As with African-Americans, this increase in risk of graft loss over a 3-year period was less than what incurred with choice of cyclosporine-based immunosuppression (1.42) versus tacrolimus (1.0).

## CREG MATCHING

Because it has been suggested that matching of cross reactive antigen groups (the so-called CREGs or public determinants) can be more discriminating,[6,7] we examined the effect of the CREG match in the 31,291 UNOS cases. The computer program of Takemoto et al[6] was used to convert the conventional HLA phenotypes to CREGs.

We began with a distribution study (Table 3). Because CREG matching is directly derived from HLA phenotypes, the 2460 zero HLA mismatched UNOS cases were by definition also CREG matched (a 100% yield). However, with the succession from one to four HLA mismatches, the CREG match yield fell to 35%, 10%, 2.5%, and less than 1% in the respective tiers. There were no CREG matches in the five and six HLA mismatched categories (Table 3).

The overall yield of CREG matches from the one to five HLA population in which 90% of the UNOS recipients fell was only 3.6%. These CREG-matched organs had gone to only 3.2% of the 7937 African-Americans who did not get a zero HLA mismatched kidney (Table 4). The yield rate was only 4.3% of the comparable 20,894 "all others" (Table 4).

The next question was whether the CREG-matched kidneys were associated with an improved graft survival in the miniscule fraction of the patients in which they were used. This analysis is being reported in detail elsewhere.[3] Interpretation of the results in the African-American recipients was undermined by inexplicable findings. The 81 CREG-matched patients from the one HLA mismatch tier (Table 4) had a nearly 10% higher graft survival at 3 years than the 174 zero HLA mismatched patients (Table 1) who by definition also were CREG matched. Survival should have been essentially the same. In addition, CREG mismatched patients from the pooled two to four HLA incom-

**Table 3. CREG Matched Cases (31,291)**

| HLA mismatches | CREG Match/Mismatch | |
|---|---|---|
| 0 | 2460/2460 | 100% |
| 1 | 471/1334 | 35.3% |
| 2 | 416/4008 | 10.4% |
| 3 | 206/8071 | 2.6% |
| 4 | 57/8542 | 0.7% |
| 5 | 0/5197 | 0% |
| 6 | 0/1679 | 0% |

For one to five HLA mismatches, CREG match yield (N = 1150) was 3.6%.

**Table 4. CREG-Matched Cases in Different HLA Mismatch Tiers**

| African-American | HLA mismatches | All Others |
|---|---|---|
| 174/174 (100%) | 0 | 2286/2286 (100%) |
| 81/206 (39.3%) | 1 | 390/1128 (34.6%) |
| 172/5485 (3.1%) | 2–4 | 507/15136 (3.3%) |
| 0/2246 (0%) | 5,6 | 0/6034 (0%) |
| CREG Match Yield Other Than 0 HLA Match | | |
| 253/7937 (3.2%) | | 897/20894 (4.3%) |

patibility tiers actually did better than patients who were CREG matched.[3]

In the "all other" population, no distinction could be made between the CREG matched and mismatched patients in any of the one to four HLA defined tiers, all of which had graft survival below the zero HLA mismatch standard, as expected.[3]

## DISCUSSION AND CONCLUSIONS

Three conclusions are justified about the use of HLA matching as an instrument of organ distribution. First, short of a zero mismatch, allocation of primary cadaver kidneys by graded HLA incompatibility scoring has little effect on overall short- or long-term graft survival. Second, the current allocation policies prejudice the candidacy of African-Americans and other hard-to-match populations. Third, tacrolimus-based immune suppression influenced outcome more than the cumulative effect of all HLA mismatches beyond the first one.

There was no clear evidence that CREG matched primary cadaver kidney allografts survived better than CREG mismatched kidneys (reported elsewhere[3]). Furthermore, the distribution study described showed that CREG matching, even if predictive of outcome, would not correct organ allocation inequities. Therefore, prospective matching trials either are not justified or must be viewed as Helsinki Declaration Type I (acquisition of human knowledge) experiments. Such experiments must not be done without informed consent, specified analyses, and conditions of trial stoppage.

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