Does Human Lymphocyte Antigen Matching Improve the Outcome in Pediatric Renal Transplants?

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ABSTRACT
Adult studies have shown a high renal graft survival if the donor and recipient match for each antigen of the human lymphocyte antigen (HLA)-A, B and DR loci (six-antigen match). The 4 yr of data from the North American Pediatric Renal Transplant Cooperative Study Registry show a statistically beneficial effect of DR matching for cadaver graft outcome. No antigen matching clearly has a worse outcome, 72% at 1 yr versus those with one or more antigen matching at each loci with a 1-yr graft survival of 81% and 2-yr graft survival of 69%. The long-term improved outcome from better antigen matching suggests that cadaver donor allograft organ assignment should address both the need of the center-driven and patient-driven concepts of recipient selection to achieve the best use of this scarce resource and an improved quality of life.

Key Words: Renal transplant, pediatric, human lymphocyte antigen match, allograft outcome, graft survival

The subject for discussion for this forum is a long-standing controversial view that human lymphocyte antigen (HLA) tissue typing and complete matching of a cadaver donor to a recipient of a kidney allograft can select out superior graft results. Transplant physicians/nephrologists have often supported the "tissue typers," whereas transplant surgeons have argued that the small point difference between poorly matched kidneys is not significant and is overcome with newer immunosuppressive medications. The problem of longer ischemia times and the lack of common handling procedures and HLA typing specificities by centers with different levels of expertise outweigh any advantage of waiting and matching according to HLA typing.

Recent reports from the University of California at Los Angeles (UCLA) Tissue Typing Laboratory, working in cooperation with the United Network for Organ Sharing (UNOS) on a program of sharing kidneys for 6-antigen (HLA)-matched cadaver renal allograft recipients have suggested that well-matched kidneys shipped across the country had a statistically higher graft survival than did locally used kidneys (1,2). For pediatric allograft recipients followed in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) registry, a statistically beneficial effect of DR matching has been shown. This report presents 4 yr of data on HLA matching and cadaver graft outcome.

METHODS
The NAPRTCS is organized with a Clinical Coordinating Center, a Data Coordinating Center, and 70 volunteer participating pediatric renal centers in the United States and Canada. Since January 1987, each allograft received by pediatric recipients (≤17 yr of age) at participating centers has been reported. Information on donor and recipient HLA tissue typing, graft function, and therapy is submitted at 1 month posttransplantation and thereafter every 6 months. Standard tissue typing techniques (3) were used by each center. An allele was counted as matching only if identical known alleles were reported in both donor and recipient. This analysis did not examine for possible antigen "splits" or less well-defined or developing subtype antigen matches or phenotypes.

RESULTS
Since January 1, 1987, the NAPRTCS registry has gathered data from 68 participating centers and has examined graft survival in 857 initially registered cadaver transplants and 701 living related donor transplants. As shown in Table 1, among cadaver transplant recipients, one or more matches at the A locus occurred in 52% of the transplants with comparable figures for the B locus (43%) and for the DR locus (55%). Among living related donor recipients, the percentage of transplants with one or more known matches were 98% for the A locus, 96% for the B, and 89% for the DR locus.

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TABLE 1. Pediatric transplant data since January 1, 1987*

<table>
<thead>
<tr>
<th></th>
<th>CAD</th>
<th>LRD</th>
</tr>
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<tbody>
<tr>
<td>1 or More</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Match</td>
<td>52</td>
<td>98</td>
</tr>
<tr>
<td>B Match</td>
<td>43</td>
<td>96</td>
</tr>
<tr>
<td>DR Match</td>
<td>55</td>
<td>89</td>
</tr>
</tbody>
</table>

* Sixty-nine centers and 857 cadaver donors (CAD) and 701 living related donors (LRD) for patients having 0 versus 1 or more known matches.

TABLE 2. Relative risk of graft loss for 1 and 2 versus 0 matches

<table>
<thead>
<tr>
<th>Locus</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>1.17</td>
<td>0.25</td>
</tr>
<tr>
<td>B</td>
<td>0.79</td>
<td>0.08</td>
</tr>
<tr>
<td>DR</td>
<td>0.78</td>
<td>0.06</td>
</tr>
</tbody>
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A proportional hazards model was used to evaluate separately the effects of HLA matching among the cadaver grafts. Fitting a main effects (three parameters) model, the knowledge of the presence of a match at each HLA locus was predictive of graft survival ($P = 0.053$). In Table 2, the relative risk for graft loss for 1 and 2 matches versus no match at the A locus was 1.17 ($P = 0.25$), while for the B and DR loci the relative risks were lower, with matching, and estimated to be 0.79 ($P = 0.08$) and 0.78 ($P = 0.06$) respectively.

Modeling of cumulative renal allograft survival was developed for several different combinations of matching alleles. In Figure 1, matching for class I type antigens shows a 1-yr graft survival of 80 and 73% at 2 yr postsurgery. Other combinations were not as successful with subjects with an A match and no B match; they had the worst outcome. In the survival analysis models adjusted for other covariates, a significant interaction between the A and B loci is seen. Matching at the A locus alone is associated with increased risk, which is offset by additional matching at the B locus.

The combination of A matching with DR matching is diagrammed in Figure 2. An A match with DR matching was no different than DR matching alone, with a 1-yr graft survival of 76% and 2-yr survival of 73%. A matching alone was no different than no A match with no DR matching, with a 1-yr graft survival of 71% and 2-yr survival of 63%. In Figure 3, the curve of combining B matching with DR matching had the same fit as the graft survival curve of Figure 1 for the A with B matching, i.e., 79% at 1 yr postsurgery. Subjects without B or DR matching had graft survival equivalent to the group without A or B matching (shown in Figure 1), i.e., 69% graft survival at 1 yr.

Figure 4 displays the subgroup with a match at both the A locus and the B locus, or no match at either, and examines the effect of adding a DR antigen. The relatively short follow-up, small sample size, and nonimmunologic factors pertinent to pediatric
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Figure 3. Accumulative distribution of the percentage of allograft survival after transplant surgery for HLA-B and HLA-DR antigens (N = number of transplants observed).

Figure 4. Accumulative distribution of the percentage of renal allograft survival posttransplant surgery for HLA-A, HLA-B, and HLA-DR antigens (N = number of transplants observed).

transplantation make it difficult to assess separate time-varying effects of class I versus class II matching. What is clear is that no antigen matching clearly has a worse outcome of 72% at 1yr versus those fortunate enough to obtain one or more antigen matching at each locus, with a 1-yr graft survival of 81% and 2-yr graft survival of 69%.

DISCUSSION

The results of our 4yr of experience of monitoring outcomes of pediatric renal transplants in North America suggest a statistically significant beneficial effect of DR matching (P ≤ 0.05) when analyzing this allele with other effects unique to our pediatric-aged patients. This was also the result of our previous symposium in 1989 in a report by Drs. Alexander and Stablein, which suggested a beneficial effect of DR matching on 1-yr graft survival.

Because the sophistication of our HLA analysis is somewhat limited to the numerical identity of reported alleles, it is beneficial to review the results of recent reports of the UNOS/UCLA six-antigen-matching allograft allocation program (1,2). In 1987, all transplantation programs in the United States agreed to share kidneys for six-antigen (HLA)-matched recipients. Whenever a donor was identified anywhere in the United States, the tissue type was entered into the computer; if a matched recipient existed, the donor center was obliged to offer one of the donor's kidneys (4). The contralateral kidney was often reserved for transplantation at the transplantation program of the organ procurement center. Follow-up of transplant outcomes up to 2yr posttransplantation through a series of questionnaires up to October 1990 has shown extremely gratifying results in 604 patients, especially in 180 recipients with contralateral controls who were being transplanted for the first time (1). The results of these 180 procedures showed statistically significant outcome differences when compared with randomly matched control kidneys (Figure 5). As noted in Figure 5, statistically significantly higher graft survival was noted for the kidney that was implanted into a six-antigen-match recipient compared with the contralateral kidney grafted into a randomly matched recipient. The mean ages of the recipients were the same, and the six-antigen-match recipients had a higher number of
individuals with a mean panel reactive antibody of >80% than did the contralateral controls. The mean cold ischemia time was 27 h for the six-antigen-match recipients compared with 21 h for the controls, but mean serum creatinine values at follow-up over the 2 yr of the study were higher in the controls than in the six-antigen-match transplants.

This UNOS study has established the fact that cadaver six-antigen-matched grafts have a significantly higher survival rate than do randomly matched cadaver allografts. Each year, the program has shown continual success despite longer cold ischemia times for the transported-shared allografts and despite the fact that a greater number of the shared allografts had preformed cytotoxic antibodies of >80% at the time of transplant surgery. This study also pointed out a poor outcome in obese or pediatric-aged recipients and in allografts obtained from donors <10 yr of age. Similar data have been forthcoming from NAPRTCS reports presented at this seminar. One problem addressed by the UCLA/UNOS study was the ability of multiple laboratories to identify the large and diverse number of HLA alleles. Despite this large diversity of HLA types and a lack of common types in their study, a recent report has suggested that the six-antigen-match program should be expanded to include the second-best or one mismatch category (2). HLA typing has shown the superiority of sibling donor transplants, and the results of the sharing of six-antigen-matched allografts have now demonstrated that HLA can select out superior grafts from cadaver donors.

Dr. Paul Terasaki et al. have proposed a compromise of cadaver donor allograft organ assignment that addresses the need of both the center-driven and the patient-driven concepts of recipient selection (1). The process would allow each transplant center to keep one donor kidney to be transplanted as it sees fit, and the other would be shared in the national pool for distribution according to the UNOS point system and the six-antigen-match recipient assignment. In this manner, as many as three quarters of patients would receive kidneys with zero ABDR or zero BDR mismatches (5).

Such a system may increase the average waiting time of a cadaver recipient for a renal allograft, but with a national pool, the waiting, relative to the size of the pool, may not actually change and uncommon HLA types may have an improved chance of obtaining a well-matched organ. The marked improvement of a 1-yr graft survival from our current national average of 78% to the six-antigen-match outcome of 91% is impressive. For pediatricians who promote transplantation as the procedure of choice for children with end-stage renal disease, the maximizing of the usable life from six-antigen-matched donor kidneys and recipients is a worthwhile goal for the use of this scarce resource and makes for the best of economics and quality of life benefits.

REFERENCES