THE INFLUENCE OF HLA-A2 SUBTYPE MISMATCH ON RENAL ALLOGRAFT SURVIVAL

Recently Fleischhauer et al. (1) described the presence of HLA-B44 subtype-specific cytotoxic T lymphocytes in a patient who rejected an HLA-matched unrelated marrow graft. We have analyzed to what extent the presence of an HLA-A2 subtype in donors or recipients of HLA-A, -B-identical or -compatible cadaveric renal allograft may influence the HLA-matched kidney graft rejection. Previously, we reported that the HLA-A2 antigen can be subdivided into four subtypes by means of cell-mediated lympholysis and biochemical analysis on isoelectric focusing gels (2-4). Population studies indicated that 89% of the HLA-A2-seropositive individuals have the A2.1 major subtype, the remaining 11% may be subdivided into three A2 minor subtypes: -A2.2, -A2.3, and -A2.4 (2-4).

We have investigated whether the presence of HLA-A2 antigenic subtypes in recipients or donors of a renal allograft might have an influence on the survival of renal allografts. Of the 3000 HLA-A2-positive, HLA-A, -B-identical or -compatible cadaveric renal allografts transplanted, a total of 51 donors and 18 groups. Donors—rejector group HLA-A2-positive donor/recipient pairs, the HLA-A2 subtype and 41 recipients in the control (i.e., non-rejector) group. Be-rejectors had an HLA-A2 minor subtype significantly more often (exact P=0.032).

The strong beneficial effect of HLA-A, -B and -DR matching and effective immunosuppression makes it extremely difficult to demonstrate the significance of other factors that can increase overall renal allograft survival. Our results, which substantiate the hypothesis put forward by Fleischhauer et al. (1), suggest that HLA-A2 subtypes may exert an influence on the survival of renal allografts. When the influence of subtypes in other HLA antigens with known subdivisions—such as the HLA-A1, -A3, -B7, -B27, -B35, and -B44 antigens—is investigated, the effect of HLA-A2 antigen subtypes on graft survival may be unambiguously established.

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Table 1. HLA-A2 subtype distributions for renal allograft recipients and their donors

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Recipients</th>
<th>Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major A2</td>
<td>Minor A2</td>
<td>Major A2</td>
</tr>
<tr>
<td>Rejector group</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Nonrejector group</td>
<td>40</td>
<td>1</td>
</tr>
</tbody>
</table>

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2 Major A2 type = the A2.1 subtype; Minor A2 type = the A2.2 and A2.4 subtypes; P is for the difference in the rejectors vs. nonrejector groups.

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HUMAN HERPESVIRUS-6 INFECTION AND RENAL TRANSPLANTATION

Human herpesvirus-6 (HHV-6) infection has been recently reported in renal transplant patients (1, 2). In our study HHV-6 infection was serologically investigated by indirect immunofluorescence (Stellar Bio System IFA, Columbia, MD) in 53 renal transplant patients (39 male and 14 female) aged 12 to 64 years. All of them were under triple therapy (cyclosporine, azathioprine, and prednisone), and if acute kidney rejection occurred they were given methylprednisolone following the protocol previously described (3).

Before transplantation 40 patients (75.5%) were HHV-6-seropositive, according to data reported by Okuno et al. (2), and no correlation with age, sex, and time on dialysis was found. Antibody titers ranged from 1:20 to 1:1280, and in 31 patients (77.5%) were less than or equal to 1:80.

After transplantation 10 seronegative patients (77%) had HHV-6 seroconversion. Seven of them had received a kidney from an HHV-6-seropositive donor and 1 from a seronegative donor; for the remaining 2 recipients the HHV-6 serological status of donors was unknown. Eight seroconversions (80%)—in particular 5 of the 7 from seropositive donors—occurred during the first month.

Twenty-five seropositive patients (62.5%) had a significant increase in antibody titer as well. Eighteen of them had received a kidney from an HHV-6-seropositive donor and 4 from a seronegative donor; for the remaining 3 recipients the HHV-6 serological status of the donor was unknown. In 23 of these patients (92%)—in particular in all 18 from seropositive donors—the titer increased during the first month; in 19 (76%) antibody titers were >1:320. This frequency of active HHV-6 infection after transplantation is higher than frequencies reported by Okuno et al. (2) and lower than those found by Morris et al. (1) (66% vs. 38% and 82%, respectively).

Transmission of HHV-6 infection by transplanted organs is open to discussion (1, 4, 5). We observed that all seronegative patients who received a kidney from a seropositive donor had HHV-6 seroconversion; furthermore, 11/13 (84.6%) pairs of patients who received a kidney from the same seropositive donor reacted in the same way: in 2 pairs neither had any infection and in 9 pairs both had active HHV-6 infection. Only in the remaining 2 pairs of patients did the members react in a different way: one had HHV-6 active infection while the other had no infection. This suggests that the transmission of the infection depends more on the degree of infectivity of the transplanted organ than on the susceptibility of the recipient as previously hypothesized for CMV infection (6).

With regard to CMV infection, 48/53 patients (90.6%) were seropositive before transplantation. After transplantation, 2/48 (40%) seroconversions and 34/48 (70.8%) significant increase in CMV antibody titer were observed. Both seroconversion occurred during the second month after transplantation, in 24/34 (70.6%) of the increases in antibody titer were between the second and third months. These variations in CMV serological status occurred later than those in HHV-6, suggesting no relation between these two infections.

Okuno et al. (2) reported a close connection between virus activation and acute kidney rejection. In our study rejection occurred in 11 (20.7%) patients, and in 8 of them (72.7%) occurred during the first two months after transplantation affecting 9/35 (25.7%) patients with active HHV-6 infection and 2/18 (11.1%) patients without infection; notwithstanding the higher frequency of rejection in patients with an active HHV-6 infection, no significant correlation could be demonstrated ($P=0.2144$).

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