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HLA HISTOCOMPATIBILITY AND LIVER TRANSPLANT SURVIVAL

Bernd H. Markus*, John J. Fung, Robert D. Gordon,
Marian Vanek, Thomas E. Starzl, and Rene J. Duquesnoy

From the Department of Surgery and the Division of Clinical Immunopathology, University of Pittsburgh, Pittsburgh, Pennsylvania

Correspondence to: Rene J. Duquesnoy, Ph.D.
Div. of Clinical Immunopathology
One Children's Place, Room 5725
3705 Fifth Ave. at DeSoto St.
Pittsburgh, PA 15213-3417

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INTRODUCTION

Although the importance of HLA in kidney and probably in heart transplantation (1-5) is recognized, the role of HLA in liver transplantation remains uncertain. Earlier studies at our institution could not show a beneficial effect of HLA compatibility on liver transplant survival (6,7). Also, the degree of pretransplant sensitization measured by panel-reactive antibody nor a positive crossmatch for donor-specific preformed antibody was associated with diminished liver transplant survival (8-10). In fact, our experience with combined liver-kidney transplants suggests that preformed donor-specific antibodies can be removed from the circulation by the liver allograft without apparent adverse effects and that the subsequent kidney transplant functions well without any evidence of hyperacute rejection (11). Studies by others have suggested that in certain instances, the liver allograft may undergo hyperacute rejection (12). Presensitization and donor-specific positive crossmatches have also been shown to be associated with increased incidence of "vanishing bile duct" syndrome in liver transplant recipients (13). Studies in our laboratory on liver transplant biopsy grown lymphocytes have shown the presence of alloreactive T cells specific for donor HLA antigens (14,15).

We have recently reexamined the question of donor HLA compatibility and liver transplant survival. Our results have confirmed our previous findings that serologically defined HLA compatibility is not associated with improved liver transplant outcome. In fact, our data seem to suggest an opposite effect.

MATERIALS AND METHODS

Between March 1980 and December 1985, 667 orthotopic liver transplants were performed. 517 patients received first allografts, while second and third transplants were done in 150 patients. All patients have been followed through August 15, 1986 and received cyclosporine and steroids as immunosuppressive drugs. As of December 1984 OKT3 monoclonal antibody therapy has been added to treat acute rejection episodes. Tissue typing was done retrospectively and played no role in recipient selection.

The age range of patients was 4 months to 67 years (mean 25.3 + 18.1 SD years) including 310 adults given 385 grafts and 210 children given 282 grafts. The most common primary indications for liver replacement were cirrhosis (25.0%), biliary atresia (20.3%), primary biliary cirrhosis (17.2%), inborn errors of metabolism (13.0%), sclerosing cholangitis (8.1%) and primary liver tumors (3.9%).

Actuarial graft survival for different patient groups, who received liver transplants with various degrees of HLA compatibility, was calculated by the life table method. Criteria for transplant failures included patient death and allograft removal regardless of graft function. Statistical analysis of survival rates was done by the Breslow (generalized Wilcoxon) and Mantel-Cox (generalized Savage) tests using the BMDPC software package (11). The Breslow test is weighted toward earlier events and the Mantel-Cox test is weighted toward later events.

RESULTS

Complete typing data for HLA-A and HLA-B antigens was available for 332 donor-recipient pairs, 258 of which had primary transplants. Actuarial one year survival of primary grafts with no mismatch at the HLA-A locus (n=21) was 33.0%, with one mismatch (n=101) 60.8%, and with a complete mismatch (n=136) 58.7% (Figure 1). The survival of liver allografts with zero HLA-A antigen mismatches was less than those with one or two HLA-A antigen mismatches (Breslow p=0.125, Mantel-Cox p=0.054). HLA-B typing data showed 57.8% survival of allografts with one mismatch (n=50) and 57.4% survival for allografts with two mismatches (n=204). Only 4 patients received a liver with zero HLA-B mismatches and the one year graft survival was 50%. The numbers of transplants was too small for statistical analysis of HLA-B compatibility differences in these groups.

For 292 donor-recipient combinations, we had complete typing data for HLA-DR antigens, 224 of which were primary transplants. Actuarial one year graft survival with zero DR mismatch (n=17) was 41.2%, whereas one DR mismatched (n=62) and two DR mismatched (n=145) liver allografts had one year survivals of 56.0% and 59.7%, respectively (Figure 2). Statistical analysis showed that zero DR mismatched liver transplant had borderline significantly lower survival rates than one and two DR mismatched liver transplants (Breslow p=0.053; Mandel-Cox p=0.066).

DISCUSSION

This study confirms a previous report that HLA compatibility has no beneficial effect on liver transplant survival. In fact we observed a trend that at least for HLA-A and HLA-DR, compatibility might be associated with a decreased survival of liver allografts. The statistical analysis of differences reached borderline levels of significance, but a larger group of patients is needed before definite conclusions can be made about possible adverse effects of HLA compatibility on liver transplant outcome. Nevertheless, our findings are compatible with recent observations by others of an association between HLA

incompatibility and liver transplant dysfunction due to "vanishing bile duct" syndrome (13).

Although the findings reported here, must be considered preliminary, we have considered various explanations why HLA compatibility might adversely affect liver transplants. A consideration is that liver transplants may be physiologically and anatomically different from other solid organ transplants. This is apparent from the high success rate of liver transplants from crossmatch positive donors suggesting perhaps the relative resistance of the liver allograft to the deleterious effects of donor-specific antibody. Liver transplant recipients experience acute rejection episodes and functional studies on biopsy grown lymphocytes have shown that lymphocytes infiltrating liver transplants recognize donor HLA antigens (14,15). In analogy to other organ transplants, it is reasonable to postulate that HLA antigens are involved in liver transplant rejection.

On the other hand, additional immunological effector mechanisms unrelated to rejection, may contribute to irreversible liver dysfunction. These cellular immune reactions may have viral and autoimmune etiologies. An important consideration is the nature of the primary disease of many liver transplant recipients. In this regard HLA, may through its ability to function as a restriction element (16) promote the recipient's immune response to viral or autoantigens, thereby causing increased dysfunction of an HLA compatible liver allograft. This would explain why HLA compatible liver transplants may show under certain circumstances inferior survival. Thus, HLA compatibility may have a dualistic effect on liver transplant outcome, on one hand it may reduce rejection whereas on the other hand, it may enhance other cellular immune mechanisms leading to graft dysfunction.

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FIGURE LEGENDS

Figure 1: Actuarial survival for 258 primary liver transplants for which tissue typing data of the HLA-A locus was available.

Figure 2: Actuarial survival for 224 primary liver transplants for which tissue typing data of the HLA-DR locus was available.

FIGURE 1:

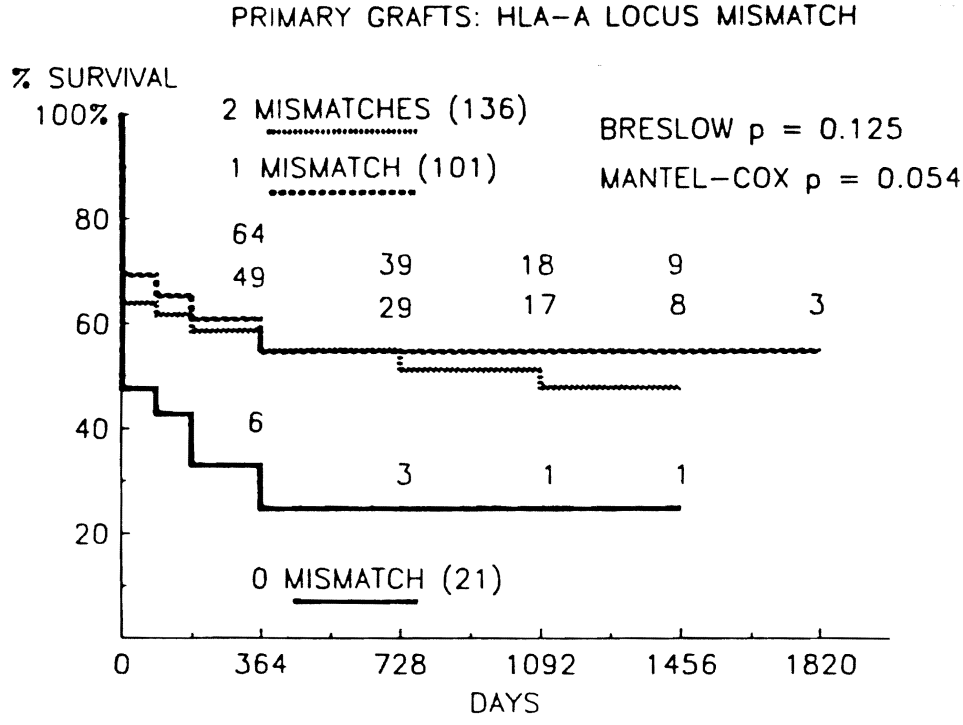

FIGURE 2: