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Association of HLA Compatibility and Decreased Liver Transplant Survival

B.H. Markus, R.J. Duquesnoy, R.D. Gordon, J.J. Fung, M. Vanek, G. Klintmalm, C. Bryan, D. Van Thiel, and T.E. Starzl

HLA COMPATIBILITY has been widely recognized to improve the outcome of kidney[1,2] and probably heart transplants[3] but no beneficial effect has been reported for liver transplants.[4-6] Neither pretransplant HLA-specific antibodies nor a positive donor-specific crossmatch seems to decrease liver allograft survival.[7-9] Recent studies have shown HLA-specific alloreactive T cells in lymphocyte cultures grown from hepatic allografts, providing evidence that HLA antigens are involved in cellular immune mechanisms leading to rejection of liver allografts.[10,11] We have recently reexamined the question of whether HLA compatibility influences liver transplant survival. This paper briefly summarizes the results of this analysis, a more detailed report will appear elsewhere.[12]

METHODS AND RESULTS

This study was conducted on more than 500 primary grafts and retransplants. The overall actuarial graft survival was 59% at 1 year and 55% at 2 years. We observed that HLA compatibility was associated with lower survival rates of liver allografts. For the HLA-A locus, liver transplants with zero mismatches (n = 42) did worse than those with one or two mismatched antigens (n = 532). One-year graft survivals were 41.1% and 61.6%, and 2-year graft survivals were 37.5% and 56.7%, respectively. The differences between the zero *v* one and two HLA-A mismatch groups were statistically significant. Although a similar trend was noted for HLA-B compatibility, insufficient numbers of zero HLA-B antigen mismatches were available for a meaningful statistical analysis.

Similarly, liver transplants with zero HLA-DR mismatches shared lower survival rates than the group with one and two HLA-DR mismatches. The 1-year and 2-year graft survivals were 51.9% *v* 60.3%, and 45.0% *v* 56.9%, respectively.

This study also considered a group of allograft failures in patients who were retransplanted. A total of 119 failures were classified into three diagnostic categories based on clinical and pathologic assessment as previously described.[13] These were rejection (n = 53), primary nonfunction (n = 31), and other causes of failure including vascular thrombosis, infections, and "technical" complications (n = 33). The frequency of rejection as the cause of transplant failure was the lowest in liver allografts with zero mismatches, especially for HLA-DR, but also for HLA-A and HLA-B. Increased HLA incompatibility was associated with higher incidence of rejection. On the other hand, primary nonfunction occurred relatively more often with HLA-DR compatible liver transplants, whereas the incidence of other causes of liver allograft failure was associated with HLA-A– or -B–compatible liver transplants.

DISCUSSION

These data demonstrate that HLA compatibility is associated with a decreased survival of liver transplants. The effect was noted for both class I antigens of HLA-A and class II antigens of the HLA-DR locus. The present findings are in contrast to the widely reported beneficial effect of HLA compatibility on kidney transplant outcome.[1,2]

Our inability to demonstrate a beneficial effect of matching for HLA on liver transplant survival does not necessarily conflict with the concept that HLA influences transplant rejection of liver allografts. This is apparent from our observations that the frequency of liver transplant failures due to rejection correlated with the degree of HLA mismatching, especially for HLA-DR. Besides transplant rejection induced by HLA

From the Division of Clinical Immunopathology and the Department of Surgery, University of Pittsburgh, and the Baylor University Medical Center, Dallas.

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Address reprint requests to Rene J. Duquesnoy, PhD, Division of Clinical Immunopathology, University of Pittsburgh, Children's Tower, Room 5725, Pittsburgh, PA 15213-3417.

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incompatibility, other immunologic mechanisms may be responsible for liver transplant failure. These mechanisms could be specific for a variety of antigens, including viral antigens, autoantigens, and tissue-specific components.

Particular consideration must be given to the influence of HLA, especially in view of its role in cellular interactions during the immune response. This phenomenon is referred to as major histocompatibility complex (MHC) restriction and has been widely observed in human and animal models of immune responsiveness. Many cellular interactions during the immune response are HLA restricted, that is, they are efficient only if the cells involved express shared HLA antigens. This MHC restriction (or self-recognition) has been demonstrated in interactions between antigen-presenting cells and T lymphocytes and in cytotoxic T cell-induced lysis of virus-infected and other antigen-expressing target cells. HLA restriction has been demonstrated for cellular immunity to clinically relevant viral antigens such as hepatitis B virus, cytomegalovirus, and Epstein-Barr virus.[14-16] During infection, cytotoxic lymphocyte-mediated damage would probably be more efficient if infected target cells in the allograft express compatible HLA antigens.

The phenomenon of HLA restriction has not been extensively studied in autoimmune liver diseases because the antigens involved are largely undefined. However, HLA has been indirectly implemented through its association with several liver diseases including chronic active hepatitis and sclerosing cholangitis.[17] These processes would not only affect the original liver, but also may contribute to recurrent disease of the transplanted liver, especially from an HLA-compatible donor.

Thus, the concept should be raised that HLA compatibility may have a dualistic effect on liver transplant outcome: On one hand it reduces the rejection process, whereas on the other hand, it may enhance other immunologic mechanisms leading to allograft dysfunction.

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