

Association Between Donor-Recipient HLA-DR Compatibility and Cytomegalovirus Hepatitis and Chronic Rejection in Liver Transplantation

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PREVIOUS studies in liver transplant patients have demonstrated that liver allografts matched for HLA, especially HLA-DR, have lower survival rates, raising the concept that HLA plays a dualistic role in liver transplantation. HLA matching will reduce rejection but may augment other major histocompatibility complex (MHC) restricted cellular immune mechanisms of liver allograft injury.^{1,2} These mechanisms could be related to immune responses, viral infections, and autoimmune disease.

Cytomegalovirus (CMV) infection is a major pathogen for transplant patients. The mechanisms of CMV-induced graft injury involve direct viral effects and cell-mediated immune responses. Several *in vitro* studies have demonstrated that lymphocyte responsiveness to CMV-infected cells is MHC restricted.^{3,4} Therefore, we postulated that HLA antigen sharing between donor and recipient might influence the development of CMV hepatitis after liver transplantation.

In liver transplant patients CMV infection is associated with the development of the vanishing bile duct syndrome, a manifestation of chronic rejection.⁵ Also, the incidence of vanishing bile duct syndrome appears to be higher for liver transplants from donors with HLA-DR matches.² This report summarizes our studies on the influence of HLA matching on CMV hepatitis and chronic liver transplant rejection. A more detailed study will be published elsewhere.⁶

MATERIALS AND METHODS

Study Population and Immunosuppression

This study was conducted on 399 adult liver transplant patients who had survived for at least 3 months after surgery. All patients received FK 506 and the protocol of FK 506 treatment is described elsewhere.⁷ Rejection episodes were treated with steroids as a bolus or by tapered doses. Steroid-resistant rejection episodes were treated with OKT3.

Serology

Complete donor-recipient HLA-A, B, DR, DQ typing was done for 355 liver transplant cases using standard lymphocytotoxicity assays. Pretransplant CMV serological status of donor and recipient was available for 262 transplant cases.

Diagnosis of CMV Hepatitis

This study focused on CMV hepatitis rather than CMV infection of liver transplant patients. The diagnosis of CMV hepatitis was based on typical inclusion bodies or direct immunoperoxidase detection of CMV early antigen in liver biopsies.

Diagnosis of Chronic Rejection

Histological criteria for chronic rejection are described elsewhere⁸ and include lymphocytic bile duct damage in 50% or more of the portal triads, with evidence of bile duct loss and hepatocanalicular cholestasis.

RESULTS

CMV hepatitis developed in 25 of 355 liver transplant patients, 17 (68%) of which shared at least one HLA-DR antigen with the donor. In contrast, HLA-DR sharing was found in 35% of 330 patients without CMV hepatitis ($P = .005$). An HLA-DR match increased the relative risk of CMV hepatitis by a factor of 3.6. No significant associations were found between CMV hepatitis and donor-recipient sharing of HLA-A, HLA-B, and HLA-DQ antigens.

In the group of 39 seronegative patients with CMV positive liver grafts, the incidence of CMV hepatitis was 44% for HLA-DR matched grafts but only 14% for HLA-DR mismatched grafts ($P = .07$). Similarly, HLA-DR matching increased the incidence of CMV hepatitis in CMV seropositive patients from 2% to 12% ($P = .006$).

During a follow-up between 10 and 24 months after transplantation, 29 patients (8%) developed chronic rejection. An earlier onset and a higher incidence of chronic rejection was seen in the CMV hepatitis group (24% vs 6%; $P < .005$).

No significant differences were found in the incidence of chronic rejection of liver transplants matched or mismatched for HLA-A, B, DR, or DQ. However, HLA-DR sharing was associated with an earlier onset of chronic rejection in patients irrespective of CMV hepatitis status (median onset 130 days vs 356 days; $P < .01$).

DISCUSSION

The higher incidence of CMV hepatitis in HLA-DR matched liver transplants is consistent with the concept of a dualistic role of HLA. According to this concept HLA

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compatibility decreases graft rejection but may augment other cellular immune mechanisms of transplant injury, especially those mediated by MHC restricted lymphocytes.¹ In vitro studies have demonstrated HLA restricted lymphocyte responses to CMV and it is possible that similar mechanisms operate within the CMV infection of HLA compatible liver allografts. Because no associations were found with HLA-A, B, or DQ sharing, it seems that HLA-DR gene products play a critical role in the postulated HLA restricted CMV-specific cellular injury of liver allografts.

This study has shown that liver transplant recipients with CMV hepatitis experience more chronic rejection. This is consistent with the previously reported association between CMV infection and the vanishing bile duct syndrome in liver transplant patients and that HLA-DR matching of the liver donor represented an additional risk factor.⁵ Our data suggest that HLA-DR matching increases the risk of CMV hepatitis, which then leads to a higher incidence of chronic rejection.

HLA-DR matching appears associated with an earlier onset but not a higher frequency of chronic rejection. Because the HLA-DR match effect was also seen in patients without CMV hepatitis, it seems that additional HLA-DR restricted lymphocyte responses to as yet undefined antigens may contribute to accelerated chronic rejection of the liver allograft.

In summary, these results expand the concept of the dualistic role of HLA in liver transplantation. A novel aspect is that HLA-DR matching will not only increase the risk of CMV hepatitis but also accelerate chronic rejection of liver allografts. A better understanding of the different HLA-associated immune mechanisms within the liver allograft may lead to improved management strategies in hepatic transplantation.

REFERENCES

1. Markus BH, Duquesnoy RJ, Gordon RD, et al: *Transplantation* 46:372, 1988
2. Donaldson PT, O'Grady J, Portmann B, et al: *Lancet* 1:945, 1987
3. Quinnan GV, Kirmani N, Rook AH, et al: *N Engl J Med* 307:7, 1982
4. Gehrz RC, Liu NC, Eckhardt J, et al: *Transplant Proc* 23:75, 1991
5. O'Grady JG, Sutherland S, Hardey F, et al: *Lancet* 2:302, 1988
6. Mañez R, White LT, Linden P, et al: *Transplantation* (in press)
7. Fung JJ, Abu-Elmagd K, Jain A, et al: *Transplant Proc* 23:2977, 1991
8. Demetris AJ, Fung JJ, Todo S, et al: *Transplantation* 53:1056, 1992