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# Posttransplant B, Non-A Non-B, and Cytomegalovirus Hepatitis Increase the Risk of Developing Chronic Rejection After Liver Transplantation

O. Bronsther, R. Mañez, S. Kusne, W. Irish, W. Roland, A. Jain, R. Llull, A.J. Demetris, and T.E. Starzl

**C**HRONIC REJECTION is a serious complication of orthotopic liver transplantation (OLT) and is a major cause of late hepatic allograft failure. Risk factors leading to the development of chronic rejection have been identified. Two of these are lack of response to acute rejection therapy and allograft cytomegalovirus (CMV) infection.<sup>1-3</sup> However, many patients develop chronic rejection without any identifiable risk factor. Furthermore, the intrinsic mechanism involved in the development of chronic rejection is not fully understood. In general, chronic rejection is a progressive disease but there are instances where it appears to reverse or stabilize over time.<sup>4,5</sup>

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are major causes of end-stage liver disease. Both infections persist after OLT leading to recurrence of hepatitis in many patients. When the allograft is infected with either of these viruses, it may be difficult to distinguish histopathologically between hepatitis and rejection.<sup>6</sup> We postulated that development of posttransplant hepatitis B or C may influence the development of chronic rejection after liver OLT.

## MATERIALS AND METHODS

From May 1, 1987 to July 31, 1989, 738 adults underwent OLT at our institution and received cyclosporine (CyA) and steroids as primary immunosuppression. Of these patients 120 (16%) died during the first 2 months after OLT. The remaining 618 patients served as the study population with a mean  $\pm$  SD follow-up of  $1.192 \pm .493$  days. The histopathologic criteria for posttransplant hepatitis and chronic rejection have been described elsewhere.<sup>6-8</sup> To investigate whether development of chronic rejection was related to a decrease in the amount of immunosuppression given, we evaluated the level of CyA (whole blood TDX) and the doses of

CyA and steroids adjusted to weight at 30, 60, 90, 180, 360, 540, and 720 days after OLT.

## RESULTS

Table 1 shows the pretransplant diagnosis and the incidence of posttransplant B, non-A non-B, and CMV hepatitis and chronic rejection in the study population. Chronic rejection developed in 118 patients at  $528 \pm 398$  days after OLT. Three-year patient and graft survival in patients who developed chronic rejection was 68% and 55%, respectively, whereas in those patients who did not experience chronic rejection they were 84% and 82%, respectively (Kaplan-Meier:  $P < .01$ ; Figs 1, 2).

The incidence of chronic rejection in patients who did not experience B, non-A non-B, and CMV hepatitis was 13% (55 of 418). In contrast, the incidence of chronic rejection was 27% (18 of 66) in patients with CMV hepatitis, 40% (45 of 112) in patients with B, non-A non-B hepatitis, and 55% (12 of 22) in patients with both CMV and B or non-A non-B hepatitis (Chi-Square test:  $P < .0001$ ). The relative risk (odds ratio) of developing chronic rejection was 2.48 in patients with CMV hepatitis, 4.43 in B, non-A non-B hepatitis, and 7.92 in CMV and B or non-A non-B hepatitis, compared with patients who did not experience posttrans-

From the University of Pittsburgh, Transplantation Institute, Pittsburgh, Pennsylvania.

Address reprint requests to Thomas E. Starzl, MD, PhD, University of Pittsburgh, Transplantation Institute, 3601 Fifth Ave, 4 Falk, Pittsburgh, PA 15213.

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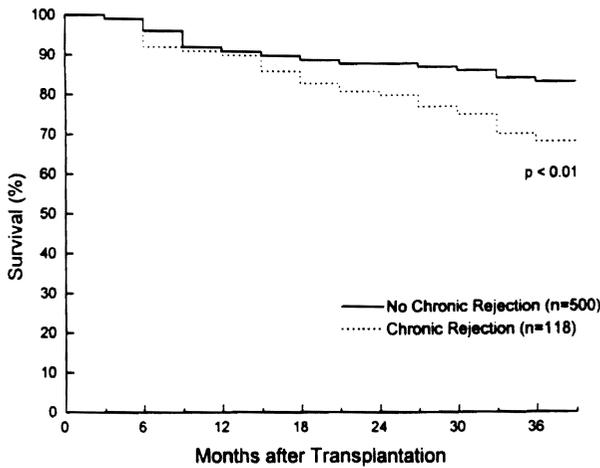
**Table 1. Incidence of Posttransplant Hepatitis and Chronic Rejection in Study Population**

	Pretransplant Diagnosis (%)	Posttransplant B/Non-A Non-B Hepatitis (%) <sup>a</sup>	CMV Hepatitis (%) <sup>b</sup>	Chronic Rejection (%) <sup>c</sup>
HBV hepatitis	43 (7)	39/43 (91)	5/47 (11)	17/47 (36)
Non-A non-B Hepatitis	64 (10)	40/64 (63)	9/67 (13)	26/67 (39)
PBC-PSC	157 (25)	14/157 (9)	20/157 (13)	25/157 (16)
PNC-E	94 (15)	6/194 (6)	18/94 (19)	11/94 (12)
Tumor	78 (13)	9/78 (12)	18/76 (23)	10/78 (13)
Cryptogenic	112 (18)	20/112 (18)	6/112 (5)	25/112 (23)
Other	70 (11)	2/70 (3)	12/70 (17)	6/70 (9)
Total	618 (100)	130 (21) <sup>d,e</sup>	88 (14)	118 (19)

<sup>a</sup>At 415  $\pm$  379 days after OLT.

<sup>b</sup>At 48  $\pm$  42 days after OLT.

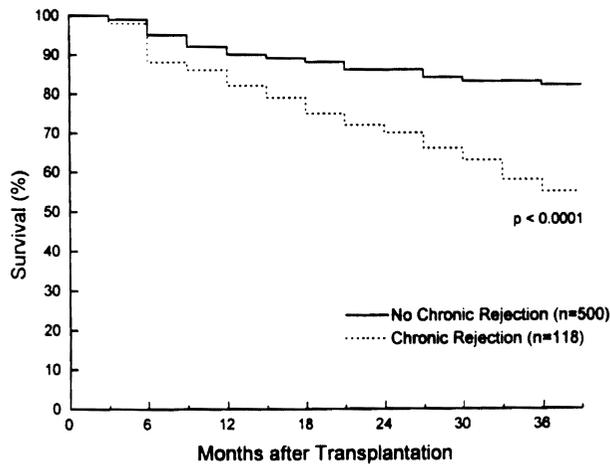
<sup>c</sup>At 528  $\pm$  398 days after OLT.



**Fig 1.** Three-year patient survival in patients with and without chronic rejection.

plant hepatitis. The incidence of chronic rejection was 35% (17 of 48) in patients with hepatitis B and 56% (46 of 82) in patients with non-A, non-B hepatitis ( $P < .05$ ). Posttransplant hepatitis was diagnosed before chronic rejection in 59% of patients, at the same time in 31%, and after chronic rejection in 10%.

Overall the immunosuppression as measured by CyA dose, level, and prednisone dose was not significantly



**Fig 2.** Three-year graft survival in patients with and without chronic rejection.

different among those patients who did or did not develop chronic rejection. Only the level of CyA at 360 days after OLT and the dose of CyA at 720 days were significantly higher in those patients who developed chronic rejection ( $P < .05$ ).

**DISCUSSION**

In the present study, the development of posttransplant B, non-A non-B, and CMV hepatitis has been associated with a significantly higher incidence of chronic rejection after OLT. We were concerned that chronic rejection had developed in patients transplanted for the diagnosis of hepatitis because of a systematic error in baseline immunosuppression. To explore this possibility we looked at the CyA dose and level and prednisone dose for patients stratified by their pretransplant diagnosis. Patients with hepatitis received equivalent immunosuppression to patients transplanted for all other indications.

On the other hand, some of the pathologic features of chronic rejection have been previously associated with hepatitis, particularly non-A non-B, in patients who did not receive transplants.<sup>9,10</sup> Thus, we must consider the possibility that HBV, HCV, and/or CMV viruses, or the cell-mediated immune responses against them, have a direct role in the pathogenesis of chronic rejection after OLT. Because there is no satisfactory therapy for HBV and HCV hepatitis after transplantation, a reevaluation of baseline immunosuppression should be considered in this high-risk population.

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