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Liver Transplantation Against T Cell-Positive Warm Crossmatches

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WE HAVE previously reported that the liver is unusually resistant to hyperacute rejection and that a positive T lymphocyte crossmatch at 37 °C (positive T-warm crossmatch) is not a contraindication for liver homotransplantation.[1-3] Since the last report,[2] we have accumulated 36 additional liver homografts transplanted in the presence of positive T-warm crossmatches. The one-year survival of these crossmatch grafts and the causes of graft loss are analyzed in this report in comparison with those of negative-crossmatch grafts.

MATERIALS AND METHODS

From March 1980 to June 1983, 137 patients with various liver disorders received 173 orthotopic liver homografts under cyclosporine and low-dose steroid therapy. Thirty-two patients received second grafts and four received third grafts. Three first grafts and two second grafts were excluded from the analyses, however, because they were ABO blood group-incompatible grafts. Thus, 134 first grafts, 30 second grafts, and four third grafts (a total of 168 grafts) were studied as of October 1983 with a minimum follow-up period of three months.

The recipients' sera obtained immediately before liver transplantation were tested for cytotoxic antibody against donor T lymphocytes at 37 °C by trypan blue dye exclusion, with a 30-minute incubation with serum and 60-minute incubation with complement. Seven serum samples that gave positive T-warm crossmatches were absorbed three times with pooled platelets of 200 randomly selected blood donors and were then retested for cytotoxic antibody against T lymphocytes of the specific liver donors. Six of the seven sera lost the T lymphocyte toxicity.

RESULTS

Incidence of Positive T-Warm Crossmatch

Among 134 first liver transplantations, 110 grafts were tested for T-warm crossmatches, but 24 were not tested because either appropriate sera or lymphocytes were not obtained. In the 110 grafts, for which the tests were performed, 22 grafts (20%) were transplanted against positive T-warm crossmatches. Among 30 second liver grafts, 11 (46%) of 24 grafts tested were transplanted against positive T-warm crossmatches. Three (75%) of the four third grafts were also transplanted against the positive T-warm crossmatches (Table 1).

The incidence of positive T-warm crossmatch increased after each liver transplantation, from 20% at the first to 46% at the second to 75% at the third grafting.

One-Year Graft Survival

Actuarial three-month survivals rates for the first liver grafts were 58% for 88 T-warm crossmatch-negative grafts, 55% for 22 T-warm crossmatch-positive grafts, and 54% for 24 grafts in which the tests were not done. Actuarial one-year survival rates for the first liver grafts were 51%, 50%, and 40%, respectively, for the crossmatch-negative, positive, and non-tested groups. There were no statistically significant differences in graft survivals among the three groups up to one year (Fig 1).

Actuarial three-month survivals of the second and the third grafts were 21% for 14 T-warm crossmatch-negative grafts, 71% for 14 T-warm crossmatch-positive grafts, and 33% for six grafts in which the crossmatches were not done. Although three-month surival of the T-warm crossmatch-positive group was better than that of the negative group, there

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Table 1. Incidence of Positive T-Warm Crossmatch for the First, Second, and Third Liver Grafts

T-Warm Crossmatch	First Graft	Second Graft	Third Graft	Total
Positive	22 (20%)	11 (44%)	3 (75%)	36 (26%)
Negative	88	13	1	102
Not done	24	6	0	30
Total	134	30	4	168

was no statistically significant difference between the two groups ($.01 < P < .05$). Actuarial one-year graft survival rates for the second and the third grafts were 21%, 44%, and 33%, respectively, for the crossmatch-negative, -positive, and nontested groups. There were no statistically significant differences among them (Fig 2).

Main Causes of Liver Graft Loss

Liver grafts were often lost to multiple causes and it is often difficult to find a single main cause of graft loss. However, the main cause of graft loss was categorized to the best of our knowledge as shown in Tables 2 and 3.

Infection was the most common cause of graft loss. Twenty-four (14%) of the 168 grafts were lost to infection, and 22 of the 24 graft losses were the result of deaths from various infections (Tables 2 and 3). When life-threatening infectious complications developed after liver transplantation, immunosuppressive therapy was decreased to a minimum or discontinued. Subsequent dysfunctions of liver grafts were often caused by rejection. When a patient died of infection with graft rejection, the graft loss was considered to be caused by infection.

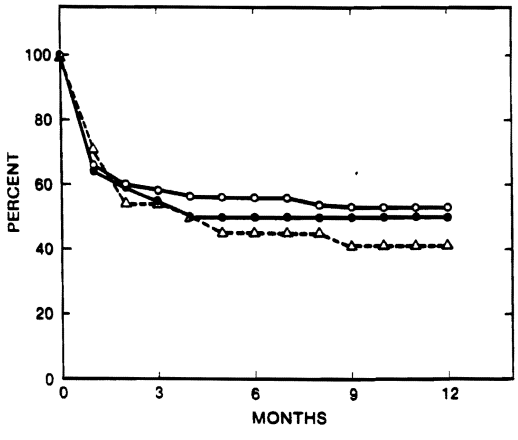

Fig 1. The actuarial survival of the first liver homografts. O—O, negative T-warm crossmatch (n = 88); ●—●, positive T-warm crossmatch (n = 22); and Δ---Δ, T-warm crossmatch not done (n = 24).

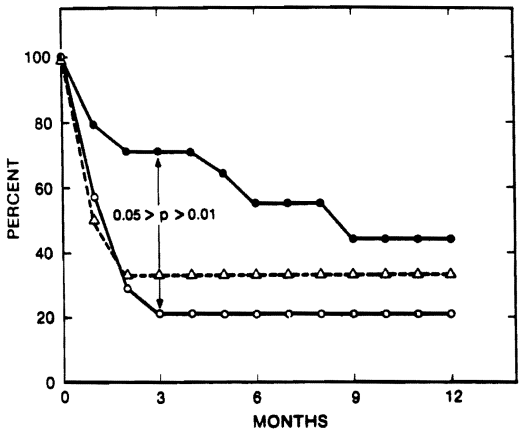

Fig 2. The actuarial survival of the second and third liver homografts. O—O, negative T-warm crossmatch (n = 14); ●—●, positive T-warm crossmatch (n = 14); and Δ---Δ, T-warm crossmatch not done (n = 6).

Rejection was the second most common cause of graft loss. Nine (10%) of the 88 primary grafts with negative T-warm crossmatch, four (18%) of the 22 primary grafts with positive crossmatch, and five (21%) of the 24 primary grafts of undetermined T-warm crossmatch were lost to rejection (Table

Table 2. Main Causes of First Liver Graft Loss

Main Cause of Graft Loss	T-Warm Negative	T-Warm Positive	T-Warm Not Tested
Operative death	5	2	3
Surgical technical complication	8	3	2
Unsatisfactory graft	8	1	1
Rejection	9	4	5
Infection	9	1	2
Others	3*	0	2†
Total number of grafts lost	42	11	— 15
Total number of liver grafts	88	22	24

*One graft loss resulting from hypoxia was caused by pulmonary arteriovenous shunt of the recipient, another from recurrent cancer, and the third from absence of adequate portal vein in the recipient.

†One graft loss resulting from death was caused by necrotizing pancreatitis and another resulted from hypoxia caused by low blood pressure before and during liver transplantation.

Table 3. Main Causes of Second and Third Liver Graft Loss

Main Cause of Graft Loss	T-Warm Negative	T-Warm Positive	T-Warm Not Tested
Operative death	0	0	1
Surgical technical complication	1	2	0
Unsatisfactory graft	1	0	0
Rejection	0	1	0
Infection	6	3	3
Others	3*	1†	0
Total number of grafts lost	11	7	4
Total number of liver grafts	14	14	6

*One graft loss resulting from hypoxia was caused by pulmonary arteriovenous shunt of the recipient and two losses resulted from death caused by cerebral hemorrhage.

†One graft loss resulted from corchitin liver necrosis.

2). The differences were not statistically significant. Only one second graft was lost to rejection (Table 3).

More than half of the grafts were lost to operative deaths, surgical technical complications such as hepatic arterial thrombosis, and unsatisfactory liver grafts either from poor selection of the donors or from graft damage during liver procurement (Tables 2 and 3).

DISCUSSION

This report reconfirms that the presence of cytotoxic antibodies against T lymphocytes of specific donors tested at 37 °C (positive T-warm crossmatch) do not cause hyperacute rejection of liver homografts. Most of the sera that were positive for T-warm crossmatch became negative after absorption with platelets. This indicates that most of the antibodies were against HLA-A and -B antigens. The mechanisms by which liver homografts escape from hyperacute rejection, as usually seen in kidney grafts against T-warm crossmatch, are still unknown. The difference in microvascular structure between the kidney and the liver (capillary sinusoidal systems) may be responsible.

The survival rate for the first liver grafts from positive T-warm–crossmatch donors was the same as that of those from negative T-warm–crossmatch donors up to one year (Fig 1). Although the survival of the second and third liver grafts with positive T-warm crossmatch was better than that of grafts with negative T-warm crossmatch (Fig 2), the number of grafts compared was small and the difference was not statistically significant.

The main causes of graft loss were similar among these groups (Tables 2 and 3). The grafts with positive crossmatches were lost to rejection as frequently as those with negative crossmatches.

CONCLUSION

At the present graft survival rate, the influence of T-warm crossmatch upon liver graft survival is not significant. Therefore, a positive T-warm crossmatch is not a contraindication for liver homotransplantation. Further investigation is needed to explain the unusual resistance of the liver graft to T-warm cytotoxic antibodies.

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