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Experience With Primary Liver Transplantation Across ABO Blood Groups

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THE LIVER has long been regarded as a privileged organ which can be transplanted across incompatible ABO blood groups with little risk of hyperacute rejection.¹ However, in a recent review of 671 first, second, and third liver transplants we found a significant advantage for ABO donor-recipient identity for primary liver transplants.² Although a large number of ABO mismatched grafts were successful, graft survival for primary liver grafts between ABO identical donor-recipient pairs was significantly better than grafts between ABO compatible but nonidentical or ABO incompatible donor-recipient pairs.

The extent to which urgency of transplantation influenced these results was not fully assessed. An urgent factor existed in many of the transplants between ABO mismatched donor-recipient pairs. We here report a review of 745 primary liver transplants performed between Jan 1, 1981 and Dec 31, 1986 at the University Health Center of Pittsburgh in which the early outcome of primary liver transplantation across ABO blood groups was assessed in relationship to the urgency of transplantation.

MATERIALS AND METHODS

Case Material

Seven hundred forty-five patients received primary liver transplants at the University Health Center of Pittsburgh between Jan 1, 1981 and Dec 31, 1986. All patients were followed through March 1, 1987. Immunosuppression was cyclosporine and prednisone as described elsewhere.³ Since December 1983, Orthoclone® OKT3 monoclonal antibody (Ortho Pharmaceuticals, Raritan, NJ) has been given for ten to 21 days for treatment of acute cellular rejection of during periods of reduced cyclosporine coverage.

Recipient selection was based on medical need, estimated liver size and body weight. Preference was usually given to ABO blood group identity except in cases of

medical urgency or donor scarcity, such as for small children. HLA typing and lymphocytotoxic cross-matching were done retrospectively and were not used in recipient selection.

ABO Blood Group Matching

The donor-recipient pairings according to ABO blood group are summarized in Table 1 and Fig 1. There were 664 ABO identical pairings. ABO mismatched transplants were divided into two classes: (1) ABO compatible but nonidentical grafts (O to A, B, or AB; A or B to AB) in which a graft-v-host (GVH) response may occur, usually manifested by a self-limited hemolytic anemia 12 to 21 days after transplantation,⁴ and (2) ABO incompatible grafts (A to B; B to A; A, B, or AB to O). There were 62 ABO compatible but nonidentical (GVH) pairings and 19 ABO incompatible pairings.

There were 333 male and 412 female recipients. There was a higher proportion (55.6%) of males in the ABO incompatible pairings than in the ABO identical (44.6%) or GVH (42.9%) pairings, but recipient sex has no influence on graft survival.

The patients ranged in age from 2 months to 76 years (mean 26.9 ± 19.4 , SD years) including 289 children (less than 19 years of age) and 456 adults. The age distribution of the patients according to ABO blood group pairings is shown in Fig 2. A higher proportion of ABO mismatched grafts involved small children for whom the scarcity of organs is always severe.

Indications for Liver Transplantation

The indications for liver replacement are summarized in Fig 3. Cirrhosis (mostly chronic aggressive hepatitis

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Table 1. Donor-Recipient ABO Matches

	Group O	Group A	Group B	Group AB
Group O	316	3	2	
Group A	21	282	2	3
Group B	18	9	57	
Group AB	3	16	4	9

but also including some cases of cryptogenic and Laennec's cirrhosis), primary biliary cirrhosis, sclerosing cholangitis, inborn errors of metabolism, and primary liver tumors were the most common indications in adults. Biliary atresia, inborn errors of metabolism, and cirrhosis were the most common indications in children. The majority of ABO mismatched transplants were performed for biliary atresia and cirrhosis, two of the most common indications for transplantation in younger patients.

Statistical Analysis

Survival analysis was performed using BMDP/PC (BMDP Statistical Software, Los Angeles, CA) on an IBM/PC-AT microcomputer.

RESULTS

Patient Survival

Early survival for the 745 patients is shown in Fig 4A and is 86.4% at 30 days at 72.4% at 180 days. Survival of patients under 4 years of age, which includes 23.5% of the recipients of ABO mismatched grafts was not different than survival of older patients (Fig 4B).

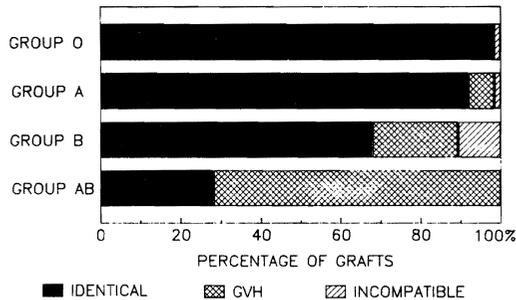


Fig 1. ABO donor-recipient compatibility classified according to recipient ABO blood group. GVH (graft-v-host) refers to ABO compatible but not identical graft-recipient pairs (such as O to A, B, or AB). Most of the ABO mismatched grafts were given to recipients of A, B, and AB blood types ■, Identical; ▨, GVH; ▩, incompatible.

NUMBER OF PATIENTS

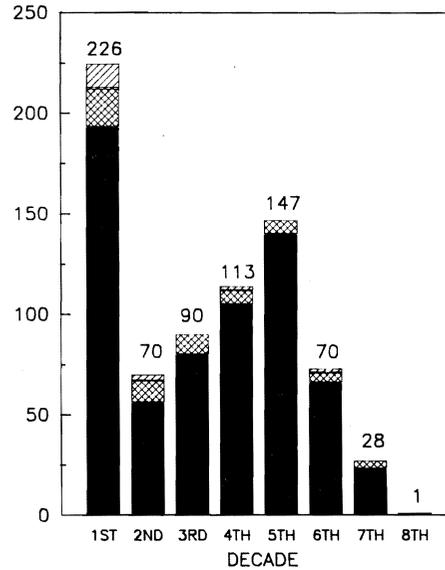


Fig 2. The age distribution of liver transplant recipients. Many of the ABO mismatched grafts were given to younger patients. ▨, incompatible; ▨, GVH; ■, ABO identical.

Graft Survival

Four hundred twenty-two (56.6%) of the 745 grafts are functioning 3 months to more than 5 years after transplantation. In 139 cases, patient death resulted in graft loss. The remaining grafts were lost when retransplantation was performed for rejection (74 cases),

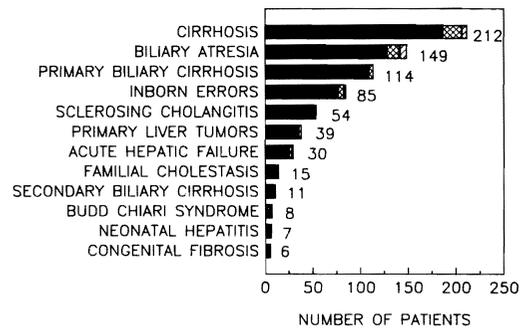


Fig 3. The major indications for liver transplantation according to ABO graft-recipient match. Most of the ABO mismatched grafts were given to recipients with chronic aggressive hepatitis (cirrhosis) or biliary atresia, the two most common indications for transplantation. ■, ABO identical; ▨, GVH; ▩, incompatible.

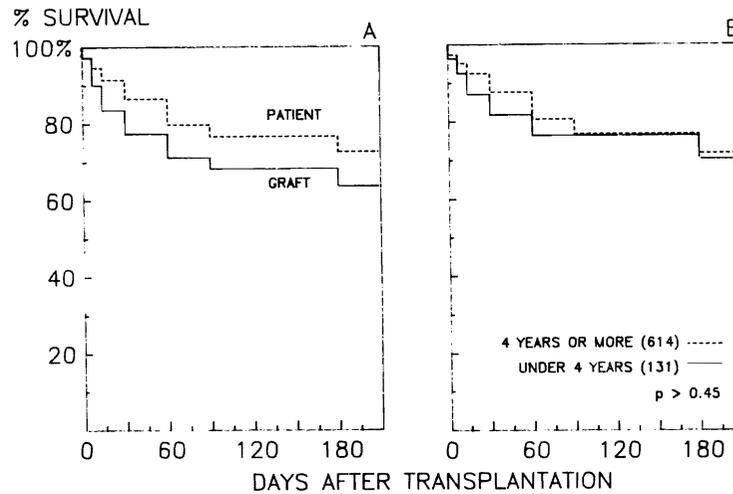


Fig 4. (A) Patient and primary graft survival for 745 liver transplant recipients. (B) Survival for recipients under 4 years of age at the time of transplantation was not significantly different than survival of patients over 4 years of age.

technical complications (63 cases), primary graft failure (44 cases), or graft infection (4 cases). 59.4% of the ABO identical grafts are functioning, compared to 40.3% of the GVH (ABO compatible but mismatched) grafts and 42.1% of the ABO incompatible grafts ($P < .04$, Fig 5).

Early survival (out of 180 days) for the 745 grafts is shown in Fig 4A. Thirty-day survival is 77.3% and 180-day survival is 63.7%. Early graft survival based on ABO match is shown in Fig 6A. Thirty-day graft survival is 79.0%, 67.2%, and 52.6% for ABO identical, GVH, and ABO incompatible pairings, respectively, and 66.0%, 46.5%, and 39.5% at 180 days, respectively. There is a highly significant

advantage in early graft survival for ABO identical grafts when compared to the two classes of ABO mismatched grafts ($P < .002$).

The Factor of Clinical Urgency

Our last effort to develop a clinical index to relate transplant outcome to pretransplant clinical risk factors such as serum bilirubin, prothrombin time, previous biliary or portosystemic shunt surgery, ascites, nutritional status and encephalopathy showed a poor correlation between outcome and risk factor score for most patients.⁵ For purposes of the present study, we considered a transplant to be urgent only for recipients with severe encephalopathy (grade 3 or grade 4), active gastrointestinal bleeding, or in intensive care at the time of transplantation. Survival of such urgent patients was significantly less than survival for other patients ($P < .01$).

Each case of transplantation between ABO mismatched donor and recipient pairs was retrospectively reviewed to determine whether or not the patient was transplanted in such urgent circumstances. For the ABO identical grafts, it was not feasible to individually review all 664 cases. However, the patient status at the time of transplantation is kept in a computer registry and it was thus possible in many of cases to determine whether or not a

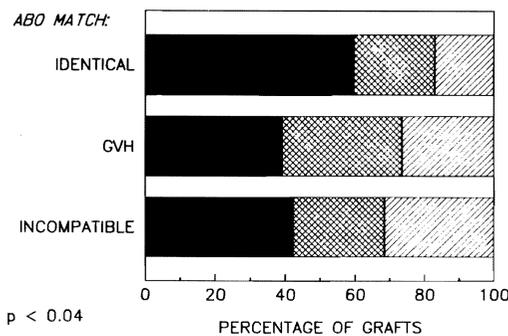


Fig 5. The fate of 745 primary liver grafts according to graft-recipient ABO match. Significantly more grafts were lost in the ABO mismatched cases. ■, functioning; ▨, retransplanted; ▩, died.

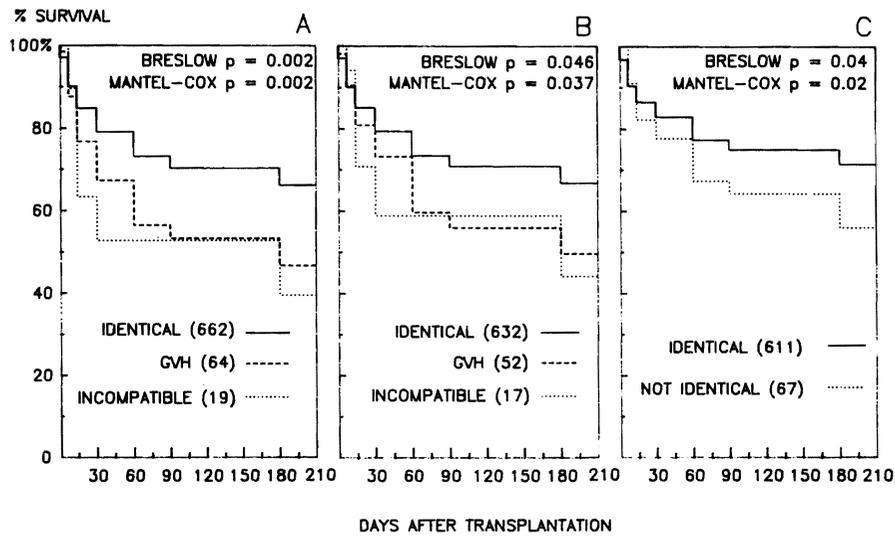


Fig 6. (A) Survival for 745 primary liver transplants based on donor-recipient ABO match. (B) Survival based on donor-recipient ABO match for primary liver transplants in patients considered clinically stable at the time of transplantation. (C) Survival based on donor-recipient match for primary liver failure with graft loss to technical failure excluded. ABO compatible but not identical (GVH) and ABO compatible donor-recipient combinations have been pooled into a single class of "not identical."

patient was in intensive care just prior to transplantation. There is a significantly higher proportion of urgent patients in the ABO mismatched graft-recipient classes ($P < .01$, Fig 7).

Figure 6B presents an analysis of the survival data when only patients considered stable at the time of transplantation are included. Even with the urgent cases removed from consideration for all the ABO mismatched (and for at least some of the ABO identical) grafts, early graft survival for ABO mismatched grafts is significantly less than survival for ABO identical grafts ($P < .05$).

Technical Graft Losses

Another possible source of bias in the data is graft loss from technical complications including hepatic artery or portal vein thrombosis or major biliary tract complications. For example, one ABO incompatible graft was lost when a patient with an anomalous superior vena cava developed fatal cerebral edema while on veno-venous bypass during the anhepatic phase of surgery. Obviously loss

of this graft had nothing to do with the ABO mismatch.

Figure 6C shows graft survival with technical graft losses removed from the analysis. The difference in survival between ABO identical and ABO mismatched grafts is not statistically significant (Breslow, $P = .11$ and Mantel-Cox, $P = .07$). However, if both classes of ABO mismatched grafts are combined, the difference in survival between ABO identical

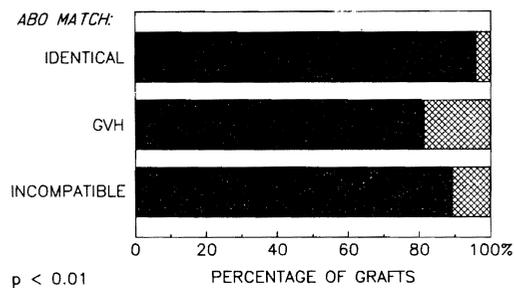


Fig 7. Donor-recipient ABO matches classified according to the clinical urgency at the time of transplantation. This is a significantly higher proportion of urgent cases in the ABO mismatched groups. ■, stable; ▨, urgent.

and ABO nonidentical grafts, with technical losses excluded, is significant ($P < .05$).

DISCUSSION

The presence of preformed antibody to donor transplantation antigens such as ABO blood group substances or to HLA antigens remains the most prohibitive barrier in renal transplantation. In liver transplantation, the frequency with which successful transplantation can be accomplished in the presence of preformed antibody to ABO blood group antigens or antidonor lymphocytotoxic antibody⁶ stands in striking contrast to the typical course of events in renal transplantation.

The results of this study support our previous report that liver transplantation across ABO blood groups is usually successful, but not without risk.² Even when the data are adjusted to remove very high risk patients, there remains a statistically significant advantage in survival for ABO identical grafts. We, therefore, continue to give preference to ABO

compatibility in the selection of liver transplant recipients, except in cases where medical urgency and donor scarcity justify taking an extra risk.

Part of the disadvantage in graft survival associated with ABO mismatched grafts may lie in the added complexity of clinical management that may result when graft-v-host disease (GVHD) is present. Inappropriate changes in therapy, especially in immunosuppression, might complicate the course of patients with ABO mismatched grafts.

In this retrospective analysis, data were not available to assess the significance of preexisting recipient anti-A or anti-B isoagglutinating antibody titers in the recipients of ABO incompatible grafts. Further studies are clearly warranted and are underway at this and other liver transplant centers. Only a deliberate prospective analysis of individual cases will clarify the nature of the increased risk of liver transplantation across ABO blood groups.

REFERENCES

1. Starzl TE, Putnam CW, Ishikawa M, et al: *Transplant Proc* 6:129, 1974
2. Gordon RD, Iwatsuki S, Esquivel CO, et al: *Surgery* 100:342, 1986
3. Starzl TE, Iwatsuki S, Shaw BW Jr, et al: *Transplant Proc* 17:250, 1985
4. Ramsey G, Nusbacher J, Starzl TE, et al: *New Eng J Med* 311:1167, 1984
5. Shaw BW Jr, Wood RP, Gordon RD, et al: *Semin Liver Dis* 5:385, 1985
6. Gordon RD, Fung JJ, Markus B, et al: *Surgery* 100:705, 1986