ANNALS OF SURGERY
Vol. 218, No. 2, 152–158

Increased Bile Duct Complications in Liver Transplantation Across the ABO Barrier

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Objective

This study evaluated the outcome of liver grafts from ABO incompatible donors, focusing on biliary complications, and compared the results to an ABO compatible control group. Also, the expression of donor ABH antigens in the liver graft was analyzed.

Summary Background Data

The outcome of liver transplantation using an ABO incompatible graft is still debated. These blood group related (ABH) antigens are known to be expressed not only on the surface of the erythrocytes, but also on the epithelial cells of large bile ducts. Because the biliary epithelium of hepatic allografts may continue to express donor ABH antigens, it may be more susceptible to immunologic bile duct injury after transplantation across the ABO barrier.

Methods

Eighteen ABO incompatible grafts were compared with 18 ABO compatible grafts in patients who were matched according to medical urgency, primary liver disease (PLD), and recipient age. After transplantation, the grafts were analyzed with cholangiography, Doppler ultrasound, or arteriography and liver histology according to protocol. Immunoperoxidase staining for ABH antigens was performed on hepatic tissue.

Results

Biliary complications developed in 82% of the ABO incompatible donors, compared to 6% of the ABO matched controls. Hepatic artery thrombosis occurred in 24%. Cellular rejection was diagnosed in 65% *versus* only 28% in the control group. The 1-year actuarial graft survival rate was 44% *versus* 78% in the control group. ABH antigens of the donor were expressed on vascular endothelium and bile duct epithelial cells as long as 150 days after transplant.

Conclusions

Using ABO incompatible allografts, a high incidence of biliary and hepatic artery complications and decreased graft survival in liver transplantation were found. An immunologic injury to the bile duct epithelium and/or to vascular endothelium is suspected.

Because uneventful orthotopic liver transplantation has been accomplished across the ABO barrier by many groups, some authors believe that the outcome of liver transplantation is not markedly affected by ABO incompatibility.[1] Others, however, have noted decreased survival and an increased number of complications.[2] Thus, debate still exists as to whether the outcome of liver transplantation is adversely affected by ABO incompatibility and, if so, whether this diminished outcome is actually related to the ABO incompatibility between donor and recipient or rather to a poor medical condition of the recipient before transplantation.

These blood group related antigens, which are named ABH, are known to be expressed not only in the surface of the erythrocytes, but also in a variety of epithelial cells in the human body.[3-4] Recent studies of ABH antigen expression in the intrahepatic biliary system demonstrated that in a normal liver these antigens are expressed mainly in the epithelial cells of large bile ducts, and that this antigenic expression is virtually absent in the epithelium of small bile ducts and hepatocytes.[5-6] We hypothesized that the biliary epithelium of hepatic allografts may continue to express donor ABH antigens and thus may be more susceptible to immunologic injury and subsequent bile duct damage after transplantation across the ABO barrier.

Our study had two primary aims: (1) to evaluate the outcome of patients receiving a transplant from ABO incompatible donors, with particular attention being paid to biliary complications, and to compare these results to an ABO compatible control group; and (2) to analyze the expression of these ABH antigens in the graft after orthotopic liver transplantation (OLT).

MATERIALS AND METHODS

Of 311 OLTs performed at our institution between March 1985 and July 1991, 18 were done with ABO incompatible grafts. An ABO compatible matched control group of 18 patients was selected according to the following criteria: (1) medical urgency (determined by the United Network for Organ Sharing [UNOS] point system)[7]; (2) primary liver disease (PLD); (3) recipient age; and (4) preservation solution because this was changed from Eurocollins (EC) Solution to University of Wisconsin (UW) Solution in July 1988. Recipient age, PLD, and recipient blood type groups are shown in Table 1.

After transplantation, bile ducts of the graft were studied according to protocol with tube cholangiography at days 10 and 21 and at 3 months. Also, when indicated, tube or percutaneous cholangiography was performed to evaluate the cause of cholestatic graft dysfunction. Liver biopsies were performed on days 0, 7, and 21 and at 3 months and with graft dysfunction. Doppler ultrasonography scans for evaluation of vascular patency were obtained on days 1, 7, and 21 and at 3 months after OLT. Arteriograms were performed when the vascular patency could not be assessed by Doppler ultrasonography. The mean follow-up time of this group of patients was 40 ± 19 months after OLT. Acute cellular and chronic ductopenic rejection was diagnosed according to standard histologic criteria.[8-9] A T-lymphocyte crossmatch was performed by the standard microlymphocytotoxic dye exclusion method with the addition of the antiglobulin technique.[10]

Immunoperoxidase staining for blood group antigens A, B, and H was performed on formalin-fixed hepatic tissue obtained from liver biopsies or from explanted grafts. The specimens were studied with commercially available monoclonal antibodies against blood group A (ER22), B (3E7), and H (92FR A2 from Dako Corporation, Carpenteria, CA). Localization of the ABO antigens was accomplished with a modification of the avidin-biotin-peroxidase complex (ABC) method, using the Vectastain ABC kit (Vector Laboratory, Burlingame, CA). Four-micron sections were deparaffinized and rehydrated to 95% ethanol. After incubation in 0.3% H_2O_2 and methanol for 30 minutes and Vectastain blocking solution (dilute normal serum) for 20 minutes, the tissue sections were sequentially incubated with the primary antibodies at 50 times dilution in 1% goat serum in phosphate-buffered saline (PBS) for 60 minutes, biotinylated goat anti-mouse immunoglobulin M (IgM) for 30 minutes, and then ABC for 30 minutes. The tissue sections were extensively washed with water between each step. Peroxidase reaction was conducted for 7 minutes in a substrate solution consisting of 50 mM of Tris buffer (pH 7.6) containing 0.1% diaminobenzidine and 0.015% hydrogen peroxide. Hematoxylin (1%) was used as the counterstain. As negative controls, normal mouse serum was substituted for the primary antibodies. Intensity of reactivity was graded on a 0–4+ scale.

Chi square analysis was used to compare dichotomous variables. Patient survival was determined by Kaplan–Meier analysis. All patients were included in the survival analysis. However, one patient in the ABO incompatible group was not included in the analysis of rejection and vascular and biliary complications owing to death 24 hours after transplantation.

RESULTS

Diffuse attenuation of the large bile ducts (Fig. 1) was found by cholangiography in 9 of the 17 grafts (53%) in

Presented, in part, at the XIII International Congress of the Transplantation Society, August 1990, San Francisco, California.
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Accepted for publication November 17, 1992.

Table 1. DEMOGRAPHICS OF AND MAJOR COMPLICATIONS OCCURRING IN BOTH GROUPS STUDIED

Age (yr)	Pres. Soln.	Blood Group Donor/Recip.	Cause of OLT	Biliary Complications	Hepatic Artery Complications	Outcome
ABO incompatible group						
51	EC	B/O	PBC	Att. ducts	Thrombosis	Re-Tx dead
33	EC	A/O	AH	—	—	Dead 19 mo post-Tx
25	EC	A/O	AH	RAL	—	Dead
43	EC	A/O	PBC	Att. ducts RAL	Thrombosis	Re-Tx dead
16	EC	AB/O	Biliary hypoplasia	Att. ducts	Mycotic aneurysm	Dead
58	EC	A/O	CAH	Anas. leak	—	Alive
52	EC	A/O	AH	Att. ducts	—	Re-Tx alive
38	EC	A/O	PGF	Att. ducts	—	Dead
18	EC	B/O	Budd-Chiari	Att. ducts	Thrombosis	Re-Tx alive
18	EC	A/O	HAT	Att. ducts anas. leak	—	Alive
19	UW	A/B	AH	—	—	Alive
46	UW	A/O	PGF	—	—	Alive
54	UW	B/A	CAH	Att. ducts	—	Dead
49	UW	B/O	PSC	Anas. leak	—	Alive
52	UW	A/O	PBC	RAL	—	Alive
61	UW	B/A	CAH	—	—	Dead
51	UW	B/O	PGF	Att. ducts	—	Alive
44	UW	B/O	Budd-Chiarl	Anas. leak	Thrombosis	Re-Tx alive
ABO control group						
56	EC	A/A	PBC	—	—	Alive
29	EC	O/O	PSC	—	—	Alive
52	EC	A/A	PBC	—	—	Alive
33	EC	O/O	AH	—	—	Alive
27	EC	O/A	PGF	—	—	Dead
17	EC	O/A	CAH	—	—	Alive
50	EC	O/A	CAH	—	—	Alive
59	EC	A/A	CAH	—	—	Dead 27 mo post-Tx
54	EC	O/O	AH	—	—	Alive
37	EC	A/A	Budd-Chiari	—	—	Alive
44	UW	O/O	PGF	—	—	Alive
17	UW	O/O	AH	Anas. leak	—	Dead
50	UW	O/O	PBC	—	—	Alive
54	UW	A/A	HAT PVT	—	—	Re-Tx alive
54	UW	A/A	PGF	—	—	Alive
34	UW	A/A	PGF	—	—	Dead
54	UW	B/B	AH	—	—	Alive
27	UW	A/A	AH	—	—	Alive

AH: acute fulminant hepatitis; HAT: hepatic artery thrombosis; RAL: recurrent anastomotic leak; PGF: primary graft failure.

the ABO compatible group, while none of the grafts in the control group showed this cholangiographic feature ($p < 0.005$) (Table 1). When present, this attenuation of the larger bile ducts could already be demonstrated at the first cholangiogram done after transplantation (day 10). Five of these nine grafts could be observed longer than 1 month; in all five, the diffuse attenuation seen in the cholangiograms at day 10 evolved to frank biliary strictures exclusively involving the donor portion of the biliary tree (Fig. 1).

Seven patients (41%) of the ABO incompatible group experienced anastomotic biliary leaks, while this complication only occurred on one graft (6%) of the control group ($p < 0.05$). Of the seven biliary leaks in the ABO incompatible group, four needed surgical repair. One duct-to-duct anastomosis was redone, while the other three were converted into a Roux-Y choledochojejunostomy. The remaining three leaks were successfully managed conservatively, as was the only anastomotic leak in the control group. In total, biliary complications (attenuation, strictures and/or anastomotic leaks) were present in 82% of the ABO incompatible donors, whereas only 6% of the ABO matched controls showed these changes ($p < 0.0001$).

Four patients (24%) in the ABO incompatible group experienced hepatic artery thrombosis (HAT), whereas

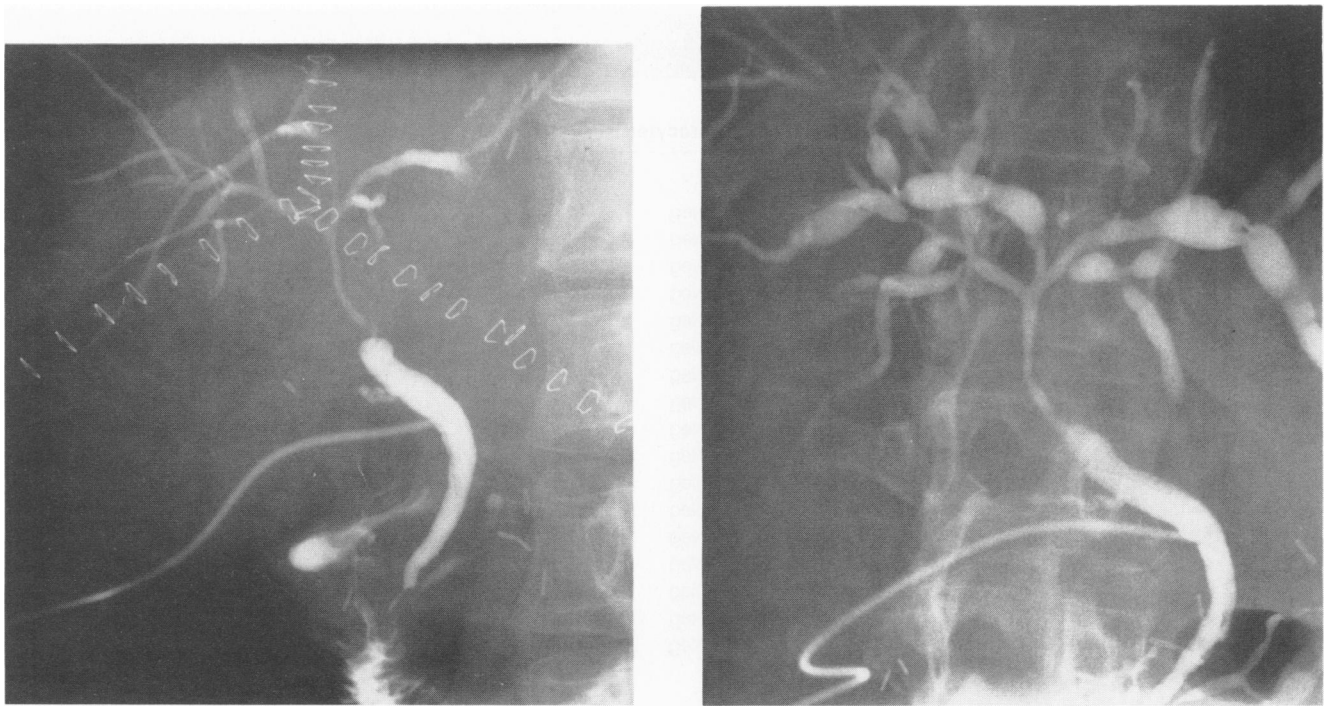

Figure 1. (A, left) Cholangiography obtained 10 days after OLT in a graft transplanted across the ABO barrier demonstrates early diffuse bile duct attenuation. (B, right) Cholangiography obtained 3 months after OLT of the same graft demonstrates late diffuse biliary strictures.

none in the control group did ($p < 0.05$). Additionally, a fifth patient in the ABO incompatible group had a mycotic aneurysm of the hepatic artery.

Cellular rejection was diagnosed in 11 grafts (65%) of the ABO incompatible group *versus* only 5 (28%) of the control group ($p < 0.05$). However, the incidence of steroid-resistant rejection requiring additional OKT_3 was similar in both groups. Ductopenic rejection was not observed in ABO incompatible grafts, and only one patient in the control group had ductopenic rejection 8 months after OLT.

Only 8 of 18 donors in the ABO incompatible group (44%) *versus* 14 of 18 (78%) in the control group survived more than 1 year ($p = 0.07$). The 1-year actuarial patient survival rate was 58% in the ABO incompatible group and 82% in the control group.

No differences were found between both groups regarding lymphocytotoxic crossmatch, percent panel reactive antibodies, or total graft ischemia time (Table 2).

For immunoperoxidase studies for ABH antigens, specimens from 12 grafts in the ABO incompatible group and 7 in the control group were used. The ABH expression on recipient erythrocytes served as a control to evaluate the expression of antigens in the grafts of an ABO incompatible donor. Transplanted livers continue to express the ABH antigens of the donor as long as 150 days after transplant (Table 3). These donor antigens were expressed in the endothelium of arteries, veins, and sinusoidal cells, as well as in the bile duct epithelial cells (Fig. 2). When present, sinusoidal ABH expression showed zonal distribution with the greatest expression being present in the periportal areas (zone 1) and no expression of these antigens in the centrilobular areas (zone 3).

The expression of ABH antigens on large (> 50 μm) sized bile ducts was noted in grafts of both the ABO incompatible group and the control group. The expression of ABH antigens on small bile ducts could be dem-

Table 2. RESULTS OF PANEL REACTIVE ANTIBODIES, LYMPHOCYTOTOXIC CROSSMATCH, AND TOTAL GRAFT ISCHEMIA TIME IN BOTH GROUPS

	IT* (min)			
	Eurocollins Solution	University of Wisconsin Solution	No. of PRA > 20%	LCM positive
ABO incompatible group	416 ± 68	583 ± 181	0/18	1/18
ABO control group	405 ± 57	649 ± 197	3/18	5/18

PRA: panel reactive antibody; LCM: lymphocytoxic crossmatch.
* Ischemia time.

Table 3. BLOOD GROUP ANTIGEN EXPRESSION IN HEPATIC ALLOGRAFTS

Blood Type D/R	Antibody	Specimen Date Post-OLT	Erythrocytes	Endothelium	Sinusoids	LBD	SBD	Hepatocyte
ABO incompatible group								
B/O	B	3 w	Neg	Neg	Neg	NA	Neg	Neg
		6 w	Neg	Neg	Neg	Neg	Neg	Neg
A/O	A	3 w	Neg	2+	1+	NA	Neg	Neg
A/O	A	3 w	Neg	2+	1+	NA	Neg	Neg
		3 m	Neg	2+	1+	3+	1+	Neg
AB/O	A	2 w	Neg	Neg	Neg	NA	Neg	Neg
	B	2 w	Neg	Neg	Neg	NA	Neg	Neg
A/O	A	3 w	Neg	1+	Neg	NA	Neg	Neg
A/O	A	4 w	Neg	2+	1+	NA	1+	Neg
		5 m	Neg	3+	2+	3+	2+	Neg
A/O	A	1 w	Neg	2+	Neg	NA	1+	Neg
		2 w	Neg	2+	2+	3+	2+	Neg
B/O	B	2 w	Neg	Neg	Neg	Neg	Neg	Neg
A/B	A	2 w	Neg	1+	Neg	Neg	Neg	Neg
A/O	A	2 w	Neg	±	Neg	NA	Neg	Neg
B/O	B	3 w	Neg	Neg	Neg	NA	Neg	Neg
A/O	A	3 w	Neg	±	Neg	NA	Neg	Neg
ABO control group								
A/A	A	4 w	2+	1+	1+	NA	Neg	Neg
A/A	A	1 w	2+	2+	1+	NA	Neg	Neg
		3 m	2+	1+	1+	NA	Neg	Neg
O/A	A	1 w	2+	Neg	Neg	Neg	Neg	Neg
A/A	A	3 w	2+	2+	2+	NA	Neg	Neg
A/A	A	2 w	2+	2+	2+	NA	Neg	Neg
A/A	A	5 m	2+	2+	2+	3+	1+	Neg
O/O	A	5 w	Neg	Neg	Neg	Neg	Neg	Neg

LBD: large bile ducts (> 50 μm); SBD: small bile ducts (< 50 μm).

onstrated in three of the ABO incompatible grafts and in one graft in the control group. Hepatocellular ABH expression was not observed in either group. The neoexpression of ABH antigens in the small bile duct epithelium may be a secondary event triggered by bile duct injury. A similar pattern of ABH expression in the small bile duct epithelium has been observed in livers with cirrhosis and biliary obstruction.[6]

DISCUSSION

Transplantation of the kidney and heart across the ABO barrier has been associated with hyperacute rejection.[11-12] Despite early reports suggesting that ABO incompatible liver grafts could be transplanted without adverse results,[13] there is now increasing evidence of diminished graft survival and rare hyperacute rejection of liver allografts.[14-15]

Liver transplantation across the ABO barrier is often done to provide a timely graft to a desperately ill patient. The poor clinical condition of the patient, however, makes the interpretation of the survival data difficult. Because especially high medical urgency and older recipient age seem to have a negative effect on survival,[7] we have incorporated these factors in the selection criteria for a matched control group. PLD has also been matched in these two groups because some PLD has been associated with poor patient outcome after OLT. In particular, fulminant hepatic failure (acute fulminant hepatitis and primary graft failure) has been associated with poor patient outcome. Thus, 7 of 18 patients (39%) in the ABO incompatible group and 9 of 18 patients (50%) in the control group had fulminant hepatic failure as PLD. This high proportion of patients with fulminant hepatic failure also underscores the high-risk group of patients analyzed in this study.

In this study, we have shown an alarmingly high incidence of biliary complications in the ABO incompatible group. These biliary complications involve only the donor biliary tree, lead to significant morbidity, and may result in retransplantation. While the results of our study imply an immune-mediated pathogenesis, the precise mechanism remains unclear. The biliary and endothelial expression of ABH antigens would make either site a potential target for an immune attack.

The cholangiographic feature of attenuation of the donor biliary tree has also been seen with HAT after trans-

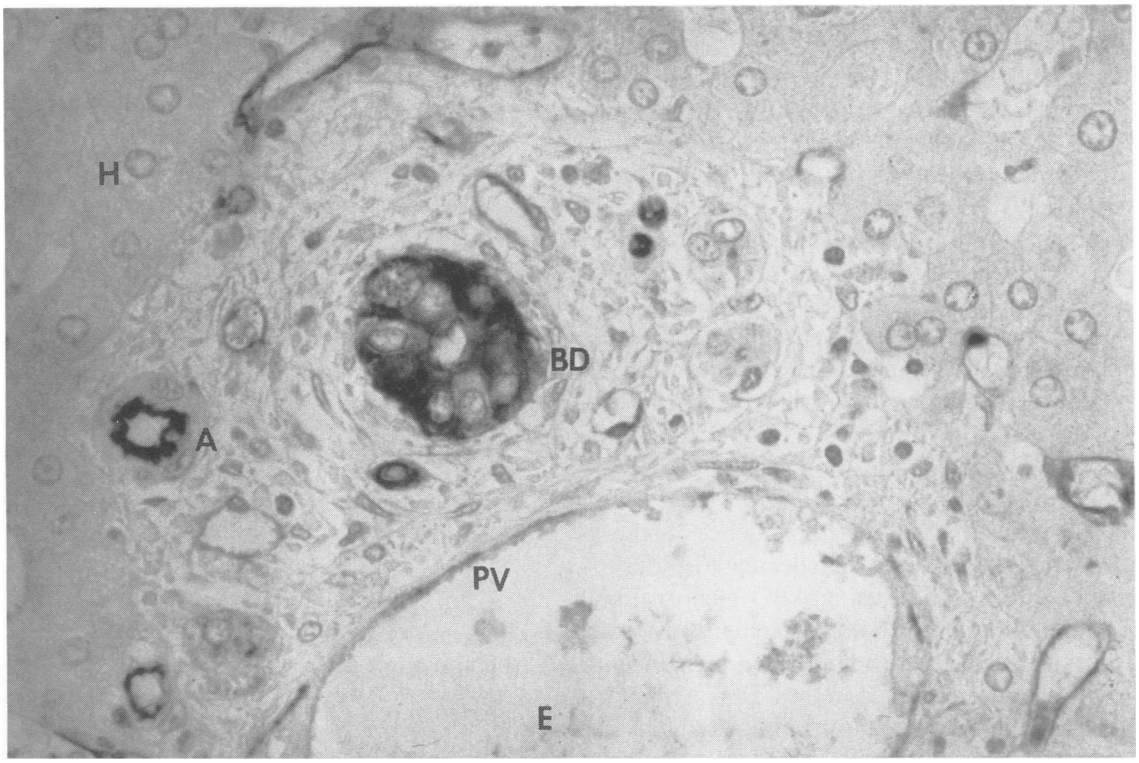

Figure 2. Immunoperoxidase stain for blood group A antigen in the setting of a donor with blood type A and a recipient with blood type O demonstrates the presence of this antigen in the epithelium of a septal bile duct (BD) and the endothelium of the portal artery (A) and vein (PV), but not on hepatocytes (H). Note the lack of staining for antigen A in recipient erythrocytes (E).

plantation and indicates ischemia of the graft. The development of severe biliary strictures later in the postoperative course is common in this setting. The possibility of continued ABH antigen expression in vascular endothelium after transplantation triggering thrombosis is supported by the observation of Demetris et al.[16] of extensive deposition of IgM and C_1q in the endothelium of the hepatic artery of ABO incompatible grafts. This could result in endothelial damage, vascular thrombosis, and, ultimately, ischemia of the bile ducts. This theory can also be supported by our observation of the increased incidence of HAT in ABO incompatible allografts, which may be caused by the same immunologic mechanisms. Thus, liver transplantation across the ABO barrier may result in an immunologic graft injury with major involvement of the hepatic artery system leading to secondary ischemia of the biliary tree.

The idea that immunologic events are likely is supported by an increased incidence of cellular rejection (60%) in the ABO incompatible group compared to the control group. Peculiarly, the 28% incidence of cellular rejection in the control group itself is markedly below the overall 60% incidence of cellular rejection in our institution.[17] This difference might be explained by the fact that the patients selected for the control group needed to be critically ill in order to match the patients in the ABO incompatible group, and therefore were less able to mount an immune response to the graft.

The decreased graft and patient survival rates in the ABO incompatible group (44% and 58%, respectively), when compared to the control group matched for medical urgency, diagnosis, and age, are consistent with the results of the UNOS Liver Transplant Registry[18] where a significant decrease in graft and patient survival (46% and 56%, respectively) was found in 105 patients with ABO incompatible grafts. Diminished graft and patient survival in patients receiving transplants with ABO incompatible grafts might not be related to the poor medical status of the patients before transplantation, but rather to the immunologic disparity of the ABO incompatible graft. This is supported by the fact that immunologic manipulation of the recipient by splenectomy, antilymphocyte globulin (ALG) anti-rejection therapy, and plasma exchange before and after operation to lower immunoglobulin levels can lead to an improved survival in ABO incompatible liver transplants.[19]

Kidney transplantation across the ABO barrier using donors of blood type A_2 has also been associated with good graft function.[20,21] This might be related to a lower cellular antigen density of the A_2 antigen, compared to the A_1 and B antigens. This phenomenon has not been studied in liver transplantation, but this might be one of

the reasons why liver transplantation across the ABO barrier can sometimes be accomplished uneventfully. Unfortunately, as it was not possible to obtain in retrospect the A blood group subtype of our donors, the possible role of the A_2 antigen could not be evaluated.

Our study confirms the observation by Gugenheim et al.[22] who also show the occurrence of late, severe, extensive biliary strictures in the grafts transplanted across the ABO barrier. We also found an increased incidence of acute cellular rejection when compared to the control group, although we have not observed differences in the severity of this type of rejection. We cannot confirm a significantly higher incidence of chronic ductopenic rejection[22] in the ABO incompatible group because we have not observed this complication in any of our 18 ABO incompatible grafts.

We have found a significantly high incidence of biliary and hepatic artery complications and decreased graft survival in liver transplantation using ABO incompatible allografts. Although an immunologic mechanism seems likely, it is unknown whether the increased incidence of bile duct complications observed in the ABO incompatible group is caused by a primary immunologic-mediated injury to the bile duct epithelium or is secondary to a vascular injury. We regard ABO incompatible allografts as a relative contraindication to liver transplantation, reserving their use for urgent, life-threatening situations.

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