

## Living related liver transplantation across ABO blood groups with FK506 and OKT3

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**Abstract.** In living related liver transplantation (LRLT), the use of graft livers across ABO blood groups is unavoidable since the organ donor is usually one of the recipient's parents. This report presents our initial experiences with LRLT, focusing on ABO-incompatible cases. From June 1990 to May 1992, we successfully performed a series of 34 LRLT on children (15 males and 19 females) ranging in age from 7 months to 15 years. Overall recipient survival rates were 90% (25/28) in elective LRLT and 50% (3/6) in emergency LRLT. These cases were classified into three groups: ABO blood group-identical ( $n = 21$ ), compatible ( $n = 10$ ), and incompatible ( $n = 3$ ). The immunosuppressive regimen consisted of FK506 and low-dose steroids in the first two groups. In the incompatible cases, exchange transfusion was performed to decrease anti-A and/or -B antibody titers before LRLT, and prophylactic OKT3 was added to FK506 and steroids after LRLT. No significant difference in recipient and graft survival was observed among the groups. In the identical group, no rejection episodes have been observed thus far. Rejection occurred in two out of the ten compatible cases. Among the incompatible cases, one recipient had mild rejection and was treated. The remaining two recipients have had no rejection episodes thus far. Although all three recipients had cytomegalovirus (CMV) infection, they were successfully treated with gancyclovir, and no lethal infection has developed in any of these cases. The present results suggest that graft livers from living related donors across ABO blood groups can function well with FK506, low-dose steroids, and prophylactic OKT3 without causing lethal complications.

**Key words:** Liver transplantation, living related – Living related liver transplantation, ABO barrier – ABO barrier, liver transplantation – FK506, liver transplantation, ABO barrier – OKT3, liver transplantation, ABO barrier

### Introduction

It is generally considered that orthotopic liver transplantation (OLT) across ABO blood groups, especially ABO-incompatible OLT, is justified in emergency cases despite the significantly lower graft survival than with ABO-identical or ABO-compatible blood grafts since, as a result of retransplantation, the recipient survival rates are similar among the groups [4, 5, 15]. In living related liver transplantation (LRLT), however, OLT across ABO blood groups is unavoidable since the organ donor is usually one of the recipient's parents. While there is no specific relationship between HLA compatibility and blood type compatibility in OLT with cadaveric donor grafts since ABO blood group antigens are inherited independently from the HLA gene complex [4, 5], in LRLT, especially that involving ABO-incompatible grafts, several factors including histocompatibility, minimum cold preservation time, immunosuppression regimen, and ABO blood groups may exert a positive effect on graft survival.

**Table 1.** Patient profile of the recipients of ABO-incompatible grafts. BA, Biliary atresia

Characteristics	Case 1	Case 2	Case 3
Age (months)/sex	8/female	21/male	23/female
Primary disease	BA	BA	BA
Type of portoenterostomy	Suruga II	Kasai	Suruga II
Donor	Mother	Father	Mother
Donor blood type	A <sub>1</sub> B	A <sub>1</sub>	A <sub>1</sub>
Recipient blood type	B	O	B
Preoperative condition			
Total bilirubin (mg/dl)	28.9	20.5	1.5
Gastrointestinal bleeding	(–)	(+)	(+)
Growth retardation	(+)	(+)	(+)
Ascites	(+)	(–)	(+)
Antiviral antibody (IgG, preoperative)			
Cytomegalovirus	(+)	(+)	(+)
Epstein-Barr virus	(–)	(–)	(+)

**Table 2.** Postoperative complications in ABO-identical, compatible, and incompatible LRLT

Complication	Incidence		
	Identical (n = 21)	Compatible (n = 10)	Incom- patible (n = 3)
<b>Surgical complication</b>			
Hepatic vein stenosis	2	0	1
Portal vein stenosis	0	0	1
Hepatic artery thrombosis	1	0	0
Biliary stenosis	2	1	0
Intestinal perforation	0	1	0
Total	5 (4 cases) 4/21 cases	2 (1 case) 1/10 cases	2 (1 case) 1/3 cases
<b>Infectious complication</b>			
Bacterial	2	1	0
Fungal	3	0	0
Viral	7	2	3
Total	12 (9 cases) 9/21 cases	3 (2 cases) 2/10 cases	3 (3 cases) 3/3 cases <sup>a</sup>

<sup>a</sup> Infection rate in incompatible groups was significantly ( $P < 0.05$ ) higher than in the compatible group

**Table 3.** Exchange blood transfusion and changes in anti-blood type antibody titer in ABO-incompatible LRLT

	Case 1	Case 2	Case 3
<b>Antibody titer (IgM/IgG)</b>			
Initial	128/4	1024/512	32/2
Operation day	8/2	16/16	16/0
Postoperatively (maximum)	16/16	16/8	8/8
<b>Exchange blood transfusion</b>			
Preoperatively (times)	4	5	2
Postoperatively	(-)	(-)	(-)

We have successfully performed a series of 34 LRLT with an immunosuppressive regimen consisting primarily of FK506 [13]. The recipients who were transplanted with ABO-identical or compatible grafts have developed only a few episodes of rejection thus far. This report presents our initial experiences with LRLT across ABO blood group barriers with FK506 and prophylactic OKT3.

### Patients and methods

From June 1990 to May 1992, we performed a series of 34 LRLT on children (15 males and 19 females, ranging from 7 months to 15 years of age) with end-stage liver disease. We had received full informed consent from their parents and the approval of the Ethics Committee of Kyoto University. Donors were selected from among the parents of the recipients on the basis of liver function tests, ABO blood group, and graft/recipient size matching [13]. Preoperative immunological evaluation included lymphocyte cross-matching, serological HLA typing, mixed lymphocyte culture reaction, and HLA-DNA typing in all recipients and their parents [8]. The surgical techniques of LRLT, including graft harvesting and implantation, have been reported elsewhere [22, 24].

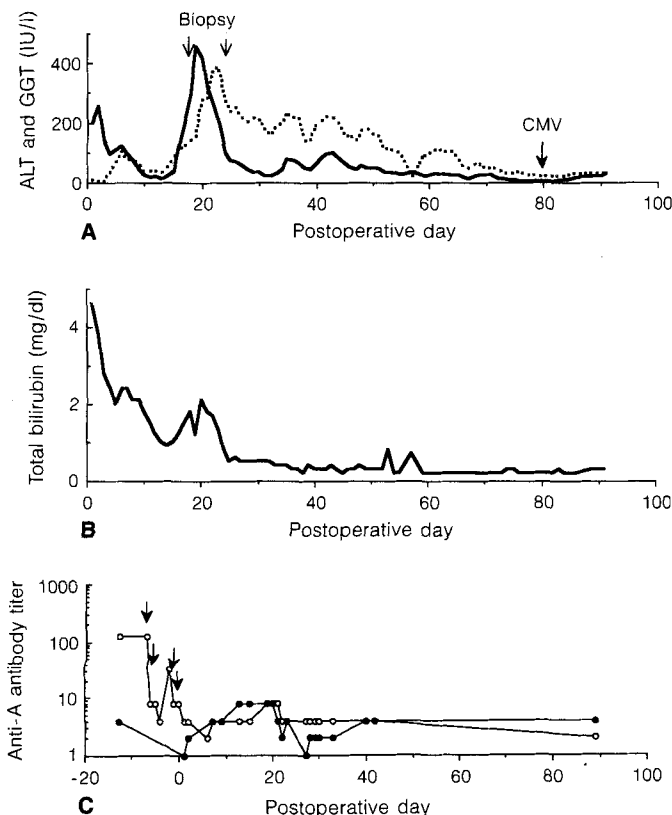
Twenty-one cases were ABO-identical, ten cases were ABO-compatible, and three cases were ABO-incompatible. In the three ABO-incompatible cases, the left lateral segment obtained from

either the father or the mother of the patient was transplanted orthotopically into the patient. Before LRLT, exchange blood transfusion was performed to decrease anti-A and/or anti-B antibody titer using washed RBC (recipient blood type and WBC-separated) and fresh frozen plasma (FFP; AB blood type). The exchange transfusion was initially performed a week before LRLT and several additional times preoperatively as needed when the antibody titer was above 64. Patient blood (20 ml) was withdrawn from the arterial access and simultaneously transfused with washed RBC (10 ml) and FFP (10 ml) through the venous access. This procedure was repeated every 3 min until the total amount of exchange was 200 ml/kg body weight. Blood cell count and plasma electrolyte levels were checked every 200–400 ml of the exchange. Calcium-gluconate and platelets were supplied as needed. In this series, we chose transfusion rather than plasma exchange and hemofiltration, taking into account the body size of the recipients and their perioperative clinical condition.

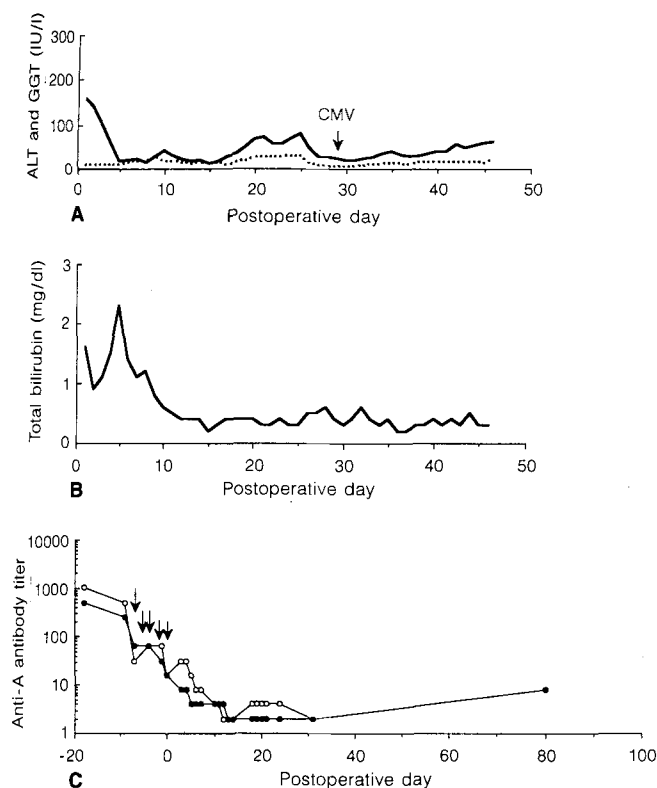
The immunosuppressive regimen consisted of FK506 and low-dose steroids [23]. Intravenous administration of FK506 initially at doses of 0.06 mg/kg per day was followed by oral administration of the same (0.3 mg/kg per day). The period of overlapping administration was several days. The FK506 dose was adjusted according to the plasma trough levels.

Methylprednisolone (10 mg/kg) was given in the operating room with steroid administration being tapered from 2 mg/kg per day to 0.5 mg/kg per day over a 7-day period. Immediately after surgery, a 10–14 day course of OKT3 (Orthopharmaceutical, N.J., USA) was started prophylactically to prevent acute rejection of ABO-incompatible grafts.

Allograft viability was assessed primarily by serial measurement of arterial ketone body ratio (AKBR) [12] and liver enzymes. Anti-A and/or anti-B antibody titer (IgM and IgG) were measured, and cellular immunity was assessed by measuring the leukocyte numbers



**Fig. 1A–C.** Time course changes in **A** ALT (—), GGT (....), **B** total bilirubin, and **C** anti-A antibody titers in case no. 1 of LRLT with an ABO-incompatible graft. Mild rejection was controlled with a steroid pulse and FK506. CMV infection was detected and treated successfully with gancyclovir. Arrows indicate exchange transfusion. —○— IgM, —●— IgG



**Fig. 2A–C.** Time course changes in **A** ALT (—), GGT (....), **B** total bilirubin, and **C** anti-A antibody titers in LRLT case no. 2 with an ABO-incompatible graft. CMV infection was treated successfully with gancyclovir. Arrows indicate exchange transfusion. —○— IgM, —●— IgG

and lymphocyte subset proportion in the peripheral blood. Acute rejection was defined as the presence of biochemical and histological abnormalities and the exclusion of other causes of graft dysfunction. Biochemical abnormalities included decreased AKBR as well as high serum bilirubin, gamma-glutamyltranspeptidase (GGT), alanine aminotransferase (ALT), etc. Histological findings consistent with rejection included cellular portal infiltration, bile duct damage, and endothelitis. Bacterial, viral, and fungal infection was detected by routine serology and culture of the blood, sputum, urine, and stool. Detection of early antigen for cytomegalovirus (CMV) in the blood and urine, as well as immunofluorescent staining of the liver biopsy specimen, were employed for diagnosis of CMV infection.

Recipient and graft survival were calculated by the Kaplan-Meier method. Statistical differences were determined using Fischer's exact test. Statistical differences in the means were determined with Student's *t*-test. A *P* value less than 0.05 was regarded as significant.

The demographic data and preoperative laboratory data of the three ABO-incompatible patients are summarized in Table 1.

## Case reports

### Case 1

An 8-month-old female (blood type B) with end-stage liver disease due to biliary atresia underwent LRLT with the left lateral segment from her father (blood type A,B). She had undergone portoenterostomy (Suruga II method) at 58 days of age and its revision at 67 days of age. Before surgery she underwent exchange blood transfusion

four times using washed RBC (blood type B and WBC-spared) and FFP (blood type AB). This procedure kept the plasma anti-A antibody titer less than 8. Immediately after reperfusion of the graft, methylprednisolone was given in the operating room, followed by intravenous administration of FK506 and steroids. Prophylactic OKT3 was given for 10 days. On postoperative day (POD) 15, she developed fever and had elevated liver function tests. Liver biopsy findings showed mild rejection, which was treated successfully with a steroid pulse and an increased dose of FK506. Local and peritoneal infections with *Staphylococcus*, *Streptococcus*, and *Pseudomonas* were successfully treated with antibiotics. At 2 months after LRLT, CMV infection was detected and treated with gancyclovir administration. She was discharged from the hospital on POD 111 with almost normal liver function and she tested negative for infection. The patient is alive and well after a follow-up of 16 months.

### Case 2

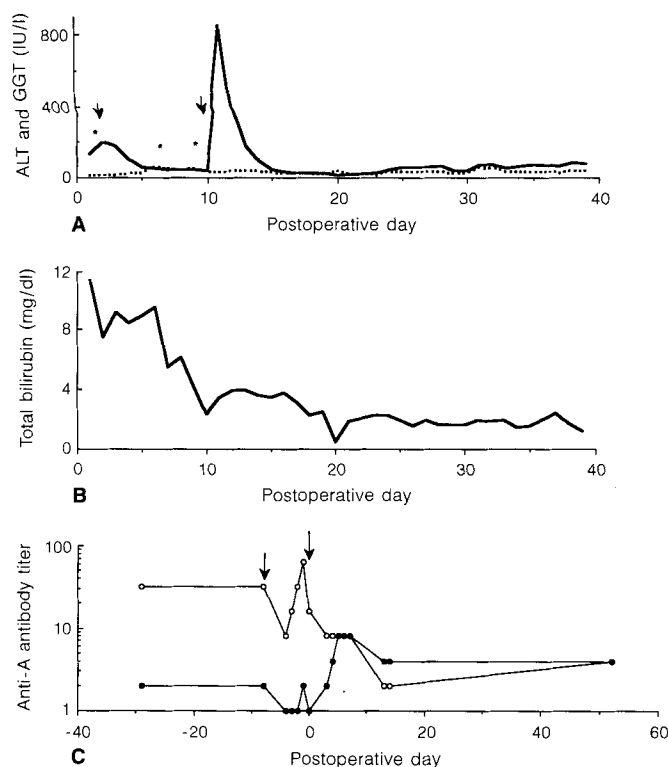
A 21-month-old male (blood type O) with biliary atresia underwent Kasai's operation at 47 days of age and revision of the procedure at 102 days. He underwent LRLT with his father (blood type A<sub>1</sub>) providing the left lateral segment for the graft. Preoperatively, exchange blood transfusion was performed five times using washed RBC (blood type O, without WBC) and FFP (blood type AB) and diluted anti-A antibody titer less than 16. He was also put on an immunosuppression regimen of FK506, steroids, and prophylactic OKT3 for 14 days. It took several months to bring his ascites under control and to improve his nutritional state. At 3 months after LRLT, systemic CMV infection was detected by early antigen test and treated with gancyclovir. On POD 124 he was discharged from the hospital with no signs of infection. He is alive and well with normal liver function and he has caught up on his growth after a follow-up of 16 months.

### Case 3

A 23-month-old female (blood type B) with biliary atresia underwent portoenterostomy (Suruga II method) at 47 days of age and revision of the same at 121 days. She underwent LRLT with the left lateral segment obtained from her father (blood type A<sub>1</sub>). Preoperatively, she had exchange blood transfusion with washed RBC (blood type B) and FFP (blood type AB) twice, which resulted in a decrease in the anti-A antibody titer to less than 8. Postoperatively, she was also placed on immunosuppression with FK506, steroids, and OKT3 for 14 days. On PODs 7 and 13, laparotomy was performed due to intra peritoneal bleeding that arose from a small artery of the graft and the hepatic artery anastomosis. She was discharged from the hospital on POD 61. Around 4 months after LRLT, her liver function test results were elevated due to stenosis of the hepatic vein anastomosis. Portal vein stenosis was also detected at 6 months after LRLT. Both were successfully dilated by transhepatic angioplasty with a balloon dilator. At 10 months, CMV infection was detected and treated with gancyclovir. She is alive and well with normal liver function tests after a follow-up of 15 months.

## Results

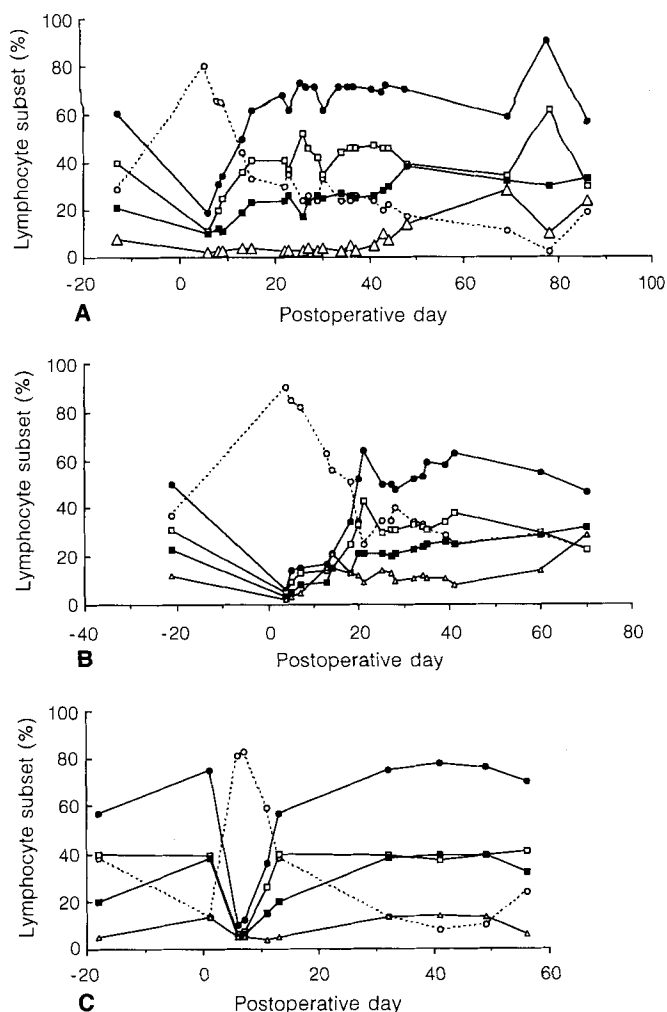
All donors were discharged from the hospital 11–17 days (mean 15 days) after surgery without any complications requiring surgical intervention and they have resumed their normal lives. None of the recipient deaths in our series was caused by surgical failure or mortality associated with graft dysfunction [4]. A total of 28 out of 34 recipients are alive and well with primary grafts after



**Fig. 3A-C.** Time course changes in **A** ALT (—), GGT (....), **B** total bilirubin, and **C** anti-A antibody titers in LRLT case no. 3 with an ABO-incompatible graft. Laparotomies (arrows in **A**) were performed due to abdominal bleeding (\*). Arrows (in **C**) indicate exchange transfusion. ○—IgM, —●—IgG

follow-up periods of between 9 and 55 months (mean 20 months). The other six recipients had functioning grafts but died of different causes, including accidental death, cardiac insufficiency, pulmonary and renal insufficiency, candida infection, multiple organ failure, and lymphoproliferative disease. One-year survival rates in both the recipients and the grafts were 72% (15/21) in the identical group, 100% (10/10) in the compatible group, and 100% (3/3) in the incompatible group. No significant difference was obtained among the groups. Three compatible cases and one incompatible case developed liver dysfunction due to rejection, whereas no definite hepatic dysfunction due to rejection occurred in the ABO-identical cases. Lymphocyte crossmatching was negative in all cases. Stimulation indices of mixed lymphocyte culture were  $3.6 \pm 3.2$  (mean  $\pm$  SD) in the identical cases,  $3.8 \pm 4.4$  in the compatible cases, and  $1.5 \pm 0.2$  in the incompatible cases. No significant difference was obtained in these values or in surgical complications among the groups (Table 2). Although all three incompatible cases had CMV infection, they were treated successfully with gancyclovir. There has been no incidence of lethal infection in these cases thus far. No retransplantation was needed for these cases after 15–16 months of follow-up.

Figures 1–3 illustrate the time course changes in clinical parameters in the ABO-incompatible cases, including routine liver chemicals (ALT, GGT, and total bilirubin) and anti-A antibody titer. Liver enzyme levels gradually returned to within the normal range except during epi-



**Fig. 4A-C.** Time course changes in lymphocyte subset populations in three cases (case no. 1 at top) of ABO-incompatible LRLT immunosuppressed with FK506 and OKT3. ....○.... B, —●— T, —□— CD4, —■— CD8, —△— NK

sodes of rejection, peritoneal bleeding, or hepatic vein stenosis. Total bilirubin declined gradually to within the normal range ( $< 2$  mg/dl) around 10 days after LRLT and has remained there ever since. FK506 trough levels were kept at around 0.1–0.3 ng/ml in the plasma and 10–30 ng/ml in the whole blood by adjusting the FK506 dose according to the daily measurement of the concentration in the blood.

Changes in anti-A antibody titer are summarized in Table 3. Preoperatively, the antibody titers ranged from 32 to 1024 (IgM) and 2 to 512 (IgG); they decreased to less than 16 with exchange blood transfusion. After LRLT the antibody titers remained less than 32 (IgM) and 16 (IgG) without exchange blood transfusion or plasma exchange.

Time course changes in lymphocyte subset proportions are shown in Fig. 4. In the initial 5–7 days after LRLT when OKT3 administration was maintained, T-lymphocyte populations including CD4, CD8, and NK cells were markedly suppressed below 10% of total lymphocytes. At the same time, the B-lymphocyte population increased over 80% of total lymphocytes. From POD 7 to POD 20, however, the proportional changes in the lymphocyte sub-

set returned to the preoperative values. After POD 20 these proportions were kept at almost the same value as observed preoperatively. The total number of lymphocytes circulating in the peripheral blood was also maintained in the normal range.

## Discussion

ABO-incompatible liver transplants are not uncommon because of the relatively low incidence of hyperacute rejection of the hepatic graft [4]. As demonstrated in recent studies, however, graft survival in ABO-incompatible liver transplantation is significantly poor, but not due to the emergency conditions in which the incompatible graft transplantations were done [5, 15]. Gugenheim et al. postulated that the poor survival of ABO-incompatible liver allografts was related to the immunological damage resulting from the presence of ABO blood group antigens in the hepatocellular components [5].

In OLT with cadaveric donor organs, the use of ABO-incompatible grafts has been justified in emergency cases as a temporary measure until a compatible graft can be found, despite the significant survival disadvantage of ABO-incompatible liver allografts. On the other hand, in our LRLT series, the ABO-incompatible graft has been unavoidable since the donor is usually one of the recipient's parents, and no other graft is available for transplantation and/or retransplantation due to the lack of social acceptance of the concept of brain death in Japan.

To avoid the disastrous chain of events resulting from antibody-mediated rejection and cytotoxic lymphocyte-mediated rejection, our strategies for ABO-incompatible LRLT are as follows:

1. To reduce antibody titer in the recipient preoperatively and postoperatively, double filtration plasmapheresis and the plasma absorption technique are applied to the recipient weighing more than 12 kg. For the recipient under 12 kg, exchange blood transfusion is chosen because the smaller body size is less suited for complicated extracorporeal circulation.
2. To eliminate the donor blood components from the graft and to protect the recipient from exposure to the donor blood cells, heparin is given to the donor systemically just before the flush perfusion, after which the graft is perfused thoroughly in a basin on the back table.
3. Prophylactic OKT3 is started immediately after the operation.
4. Based on daily measurement, antibody titer is kept below 64 using the above-mentioned methods.

Splenectomy, proposed previously for ABO-incompatible hepatic grafts [3], was not performed in our series since splenectomy has its own specific long-term septic hazards [7, 17], while its beneficial effect of inhibition of postdepletional antibody resynthesis remains controversial [1, 14].

Reinforced immunosuppression with OKT3 in addition to FK506 and low-dose steroids was adopted for LRLT with ABO-incompatible grafts since the use of this monoclonal antibody has successfully controlled the severe, acute rejection process in OLT with cadaveric donors [2] and since prophylactic OKT3 has suppressed early rejection [10].

Small children, for whom LRLT has been primarily employed, have higher risks of postoperative hepatic artery thrombosis due to the small caliber of their arteries [9, 19]. Preventing severe acute rejection with prophylactic OKT3 may also decrease the risk of hepatic artery thrombosis, another major cause of graft loss, since the rate of arterial thrombosis is thought to be related to the reduced blood flow seen in severe rejection [16] and to diffuse arterial spasm in hyperacute rejection [6].

There is concern that OKT3 prophylaxis might increase the chances of infectious complication since an increased incidence of opportunistic infection [11, 18] and lymphoproliferative disorder [21] associated with the use of OKT3 have been cited previously. However, one study reports that the use of monoclonal antibody with ABO-incompatible patients did not increase the incidence of lethal infection [15]. A recent randomized, prospective trial indicated that acyclovir and immune globulin prophylaxis were effective in preventing viral and fungal infection in liver transplant recipients receiving OKT3 [20]. In our series, gancyclovir was effective in treating CMV infection.

As a result of these procedures, the recipients with ABO-incompatible grafts successfully survived the early postoperative phase without lethal complications. Interestingly, anti-A antibody titers have remained low ( $< 16$ ) with FK506 and low-dose steroids, even after the curtailment of OKT3. As reported by others [15], prophylactic OKT3 did not seem to increase the incidence of lethal infection in our series, though its prophylactic use may have to be reconsidered in the future.

In conclusion, the present results suggest that graft livers from living related donors across ABO blood groups function well with FK506, low-dose steroids, and prophylactic OKT3 without causing lethal complications.

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