Tohoku J. Exp. Med., 1997, **181**, 139–144

Living Related Partial Liver Transplantation in Biliary Atresia: 11 Cases of Experience

HIROTAKA KATOH[1], NOBUHIRO OHKOHCHI[1], SUSUMU SATOMI[1], SATORU SHIMAOKA[2] and RYOJI OHI[2]

[1]*The Second Department of Surgery,* [2]*Department of Pediatric Surgery, Tohoku University School of Medicine, Sendai 980-77*

KATOH, H., OHKOHCHI, N., SATOMI, S., SHIMAOKA, S. and OHI, R. *Living Related Partial Liver Transplantation in Biliary Atresia: 11 Cases of Experience.* Tohoku J. Exp. Med., 1997, **181** (1), 139–144 —— Eleven children, 4 males and 7 females, with biliary atresia receiving living related liver graft were studied. The mean age was 1.8 years and the mean body weight was 10.3 kg. The donors were 4 fathers and 7 mothers. The graft was the lateral segment or left lobe. ABO blood group matching was compatible in 9 and incompatible in 2. All patients except one were crossmatch negative. Immunosuppression at induction was triple therapy (cyclosporine, azathioprine and steroid) or FK506 plus steroid. Acute rejection episodes were treated with pulse steroids. When the signs of rejection persisted despite steroid pulse therapy, 15-deoxyspergualin (DSG) was added. The survival rate of the patients was 73%. Three patients died of portal vein thrombosis, hepatic artery thrombosis and sepsis respectively. Other major complications included hyperbilirubinemia, bile duct stenosis, bile leakage and portal vein anastomosis narrowing. Complications of the donor were sepsis in one, and liver dysfunction in two. Although there are some complications related to graft size mismatch and operative procedure, living *related* partial liver transplantation is an effective therapy in countries where donor source is restricted. ——— biliary atresia; living related liver transplantation; 15-deoxyspergualin

Living-donor liver transplantation is the only way to treat children with end stage liver diseases in countries where liver graft from a cadaver donor is unavailable (Broelsch et al. 1990; Strong et al. 1990). More than three hundred living related liver transplantations have been performed for children with end stage liver diseases at five centers in Japan since 1990.

In our institute, the first living related liver transplantation was carried out in July 1991, and till May 1996 we have experienced 13 cases including 11 patients with biliary atresia. In liver transplantation, the survival rate in cases with ABO

Received June 30, 1996; revision accepted for publication November 15, 1996.

Address for reprints: Hirotaka Katoh, M.D., The Second Department of Surgery, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-77, Japan.

This paper was presented at 6th International Sendai Symposium on Biliary Atresia, May 20 and 21, 1996, Sendai.

incompatible donor was significantly worse than that in cases with ABO compatible donors. We performed two cases of ABO incompatible living related liver transplantation by the FK506-based immunosuppression protocol and obtained good results, using a new immunosuppressive drug, 15-deoxyspergualin (DSG), in steroid-resistant acute rejection. In this paper we focused on ABO incompatible liver transplantation and the effectiveness of DSG.

Patients and Methods

From July 1991 to May 1996, 11 children, 4 males and 7 females, with biliary atresia underwent living related liver transplantation at the Second Department of Surgery Tohoku University School of Medicine. The mean age at transplantation was 1.8 years, ranging from 0.5 to 5.3 years. The mean body weight of the recipient was 10.3 kg, ranging from 5.2 to 20.5 kg. All patients had previously undergone Kasai's operation.

Indications for liver transplantation in our institute has been as follows: i) continuous hyperbilirubinemia, ii) portal vein narrowing or inverse portal blood flow, iii) hypoxemia due to hepatopulmonary syndrome, iv) unsuccessful Kasai's procedure, and v) malnutrition due to hepatic failure.

The living donor was selected from the healthy parents, 4 fathers and 7 mothers, ranging in age from 28 to 42 years. The liver graft was the lateral segment or left lobe. ABO blood group matching was identical in 8 patients, compatible-nonidentical in one, and incompatible in 2. All patients except one were lymphocyte cross-match test negative.

Operative procedure in donor

The donor's lateral segment or left lobe was used as the graft. After isolation of the pedicle of the left lobe, the liver was divided at the principal plane, and the left hepatic vein was encircled at the junction to the inferior vena cava. During these procedures the vessels remained unclamped. We waited one hour before the perfusion to allow the graft to recover from the injury caused by the operation. At the graft removal, the vessels of the graft were clamped and then cut. The graft was perfused through the portal vein and the hepatic artery with 1,000 ml of University Wisconsin solution (Yamaoka et al. 1991). The warm ischemic time of the graft from the vessel clamp to the perfusion was within 2 min.

Operative procedure in recipient

In the recipient, total hepatectomy was performed preserving the retrohepatic vena cava. Partial liver graft from the living donor was transplanted orthotopically. The hepatic vein of the graft was anastomosed to the right or left hepatic vein of the recipient. The graft portal vein was anastomosed to the recipient portal trunk. In four cases with portal vein sclerosis or stenosis, stenotic portal vein was resected and the vein graft from the donor, i.e., the saphenous vein

in two cases and the ovarian vein in two, was interposed. The hepatic artery of the graft was anastomosed to the left, right or proper hepatic artery end-to-end with interrupted 8/0 nonabsorbable suture using operative microscope (Tanaka et al. 1993). The total ischemic time of the graft was 2 to 6 hr.

Immunosuppression at induction

In ABO compatible cases, the patients weighing less than 10 kg were maintained by cyclosporine-based triple therapy (cyclosporine, azathioprine and methylprednisolone) following transplantation. Patients weighing more than 10 kg were maintained by FK506 and steroids.

In cases with incompatible ABO matching or positive T cell cross-match, plasma exchange was done before transplantation to reduce the anti-A, anti-B or anti-HLA antibody, and FK506 and methylprednisolone were administered at induction.

Rejection therapy

Acute rejection was diagnosed by clinical symptoms and histologic findings of graft biopsy. Acute rejection was treated with high-dose (20 mg/kg/day) pulse methylprednisolone for 3 days. When the signs of rejection persisted despite steroid pulse therapy, DSG 3 mg/kg was given daily for a maximum of 14 days including a 3 day course of high dose of methylprednisolone. When the white blood cell count decreased below 3,000/mm^3, DSG was discontinued and synthetic granulocyte colony-stimulating factor (G-CSF) was started.

Results

Survival rate and complications in recipient

Eight of 11 patients are alive and well. The other 3 patients died of portal vein thrombosis, hepatic artery thrombosis and sepsis due to necrotizing myofasciculitis within two weeks after transplantation, respectively. The survival rate of the patients was 73%.

Late major complications were as follows: hyperbilirubinemia due to cholangitis and bile duct obstruction by bile plaque, bile duct stenosis including the anastomosis due to insufficient blood supply, bile leakage and portal vein anastomosis narrowing.

In the patient with hyperbilirubinemia, plasma exchange was performed to reduce the total bilirubin level and control bleeding tendencies. Despite of several trials of plasma exchange, her total bilirubin level was elevated up to 60 mg/100 ml, and bleeding tendencies continued for several months. Her hyperbilirubinemia finally disappeared spontaneously 5 months after the transplantation. In patient with bile duct stenosis, percutaneous transhepatic biliary drainage was performed. Dilatation with a balloon catheter was carried out and an internal metal sprint spring was set successfully through the transhepatic route.

TABLE 1. *Major complications in the recipient after living related liver transplantation in biliary atresia*

	Number of case	Treatment	Results
Major complications in the early period			
Portal vein thrombosis	1	Thrombectomy	Dead (12 days after transplantation)
Hepatic artery thrombosis	1	Thrombectomy	Dead (15 days after transklantation)
Necrotizing myofasciculitis (Sepsis)	1	Radical debridement and antibiotics	Dead (5 days after transplantation)
Late onset major complications			
Cholangitis (hyperbilirubinemia)	1	Plasma exchange	Success
Bile duct stenosis	1	Percutaneous dilatation	Success
Bile leakage	1	Continuous drainage	Waiting for re-operation
Portal vein narrowing	1	Percutaneous dilatation	Success
Total	7		

Abdominal plain x-ray, taken 6 months after the placement of the biliary sprint, showed the disappearance of the sprint. The sprint probably slipped down into the small intestine. He is doing well now without any complications. In a patient with portal vein narrowing, percutaneous transhepatic dilatation of the portal vein stricture was done successfully (Table 1).

Acute rejection

Acute rejection was recognized 11 times in 6 patients. Among them, steroid resistant rejections occurred 3 times in 3 patients. Among these patients, one was ABO compatible and two were ABO incompatible (A to O and AB to B). These steroid-resistant acute rejection episodes were successfully treated with DSG plus high dose methylprednisolone. The adverse events of DSG observed in one patient were mild leukocytopenia and thrombocytopenia, and G-CSF was used.

Course of the patient with positive T cell cross-match

In one patient with positive T cell cross-match, that was presumably associated with prior blood transfusion, plasma exchange was performed for three consecutive days before transplantation to reduce the antibody titer. The immunosuppression therapy at induction included FK506, azathioprine and steroid. She had no episode of rejection but developed bile leakage from the bile duct anastomosis, and received intraabdominal drain for continuous bile drainage.

Complications in donor

One donor had severe complications. This donor, a healthy father, donated his lateral segment as a graft. During the operation the right hepatic bile duct was cut accidentally so reconstruction was performed by Roux-en-Y hepaticojejunostomy. He had leakage from the bile duct anastomosis, and the bile duct anastomosis became stenotic 2 weeks after the operation. Sepsis due to cholangitis occurred 3 weeks after the operation, but improved by administration of antibiotics. In two other donors, slight liver dysfunction was observed after the operation. All these complications improved within several months and all donors are now alive and doing well.

Discussion

Since 1989 living related liver transplantation have been generally performed in Japan and United States. An operative procedure involving a donor is more complex than that of cadaveric donor, but the graft viability is significantly better than that of a cadaveric donor (Katoh et al. 1994). Because the results of clinical living related liver transplantation is satisfactory, living related liver transplantation was now accepted technically and ethically (Broelsch et al. 1994).

The best results for liver transplantations are achieved when ABO blood type of the donor and recipient are identical (Cecka et al. 1996). In pediatric living related liver transplantation, ABO incompatible parents are accepted for living donor in some cases (Inomata et al. 1996). In our experience, two cases of ABO-incompatible living related liver transplantations were successfully done with preoperative plasma exchange, FK506-based immunosuppression regimen, and therapy for acute rejection with methylprednisolone pulse and DSG.

DSG is the synthetic, 15-deoxy analog of the novel antibiotic spergualin. In 1994, DSG was licensed in Japan for acute renal allograft rejection (Gores 1996). In a Japanese study on steroid-resistant renal rejection, DSG successfully reversed rejection 59% of the time, compared to a rate of 62% for OKT3 (Okubo et al. 1993). Adverse events associated with DSG were primarily related to bone marrow suppression, while the side effects of OKT3 included pyrexia, gastrointestinal symptoms, and viral infections. We used DSG as a first line treatment for steroid resistant acute rejections in three living related liver transplantation recipients at a dose of 3 mg/kg daily for 4 to 14 days. All steroid resistant acute rejections were treated successfully by our protocol. These findings suggest that DSG is a new additional therapy for acute rejection in liver transplantation. We conclude that ABO incompatible living related liver transplantation can be carried out using FK506-based immunosuppression and DSG in steroid-resistant acute rejection.

In countries where cadaveric organ procurement is difficult or impossible for various reasons, living related liver transplantation is the only way to provide

viable livers (Otte et al. 1994). The results of over 300 cases in Japan suggest that even though a few complications do occur, living related liver transplantation is a promising option to overcome the graft shortage for small children.

References

1) Broelsch, C.E., Emond, J.C., Whitington, P.F., Thislethwaite, J.R., Baker, A.L. & Lichtor, J.L. (1990) Application of reduce-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. *Ann. Surg.*, **212**, 368-377.
2) Broelsch, C.E., Burdelski, M., Rogiers, X., Gundlach, M., Knoefel, W.T., Langwieler, T., Fischer, L., Latta, A., Hellwege, H., Schulte, F.J., Schmiecel, W., Sterneck, M., Greten, H., Kuechler, T., Krupski, G., Loeliger, C., Kuehnel, P., Pothmann, W. & Esch, J.S. (1994) Living donor for liver transplantation. *Hepatology*, **20**, 49S-55S.
3) Cecka, J.M., Gjertson, D.W., Ogura, K. & Terasaki, P.I. (1996) ABO, tissue typing, and crossmatching incompatibility in liver transplantation. In: *Transplantation of the Liver*, W.B. Saunders Co., Philadelphia, pp. 288-293.
4) Gores, P.F. (1996) Deoxyspergualin: Clinical experience. *Transplant. Proc.*, **28**, 871-872.
5) Inomata, Y., Tanaka, K., Egawa, H., Uemoto, S., Ozaki, N., Okajima, H., Satomura, K., Kikuchi, T., Yamaoka, Y. & Hashida, T. (1996) The evolution of immunosuppression with FK506 in pediatric living-related liver transplantation. *Transplantation*, **61**, 247-252.
6) Katoh, H., Ohkohchi, N., Hirano, T., Sakurada, M., Orii, T., Koyamada, N., Fujimori, K., Takemura, M., Endoh, T., Satomi, S., Taguchi, Y. & Mori, S. (1994) Viability of partial liver graft from living donor in pigs. *Tohoku J. Exp. Med.*, **175**, 179-184.
7) Okubo, M., Tamura, K., Kamata, K., Tsukamoto, Y., Nakayama, Y., Osakabe, T., Sato, K., Go, M., Kumano, K. & Endo, T. (1993) 15-Deoxyspergualin "rescue therapy" for methylprednisolone-resistant rejection for renal transplants as compared with anti-T cell monoclonal antibody (OKT3). *Transplantation*, **55**, 505-508.
8) Otte, J.B., de Ville de Goyet, J., Reding, R., Hausleithner, V., Sokal, E., Chardot, C. & Debande, B. (1994) Sequential treatment of biliary atresia with Kasai portoenterostomy and liver transplantation: A review. *Hepatology*, **20**, 41S-48S.
9) Strong, R.W., Lynch, S.V., Ong, T.H., Matsunami, H., Koido, Y. & Balderson, G.A. (1990) Successful liver transplantation from a living donor to her son. *N. Engl. J. Med.*, **322**, 1505-1507.
10) Tanaka, K., Uemoto, S., Tokunaga, Y., Fujita, S., Sano, K., Nishizawa, T., Sawada, H., Shirahase, I., Kim, H.J., Yamaoka, Y. & Ozawa, K. (1993) Surgical techniques and innovation in living related liver transplantation. *Ann. Surg.*, **217**, 82-91.
11) Yamaoka, Y., Ozawa, K., Tanaka, A., Mori, K., Morimoto, T., Shimahara, Y., Zaima, M., Tanaka, K. & Kumada, K. (1991) New devices for harvesting a hepatic graft from a living donor. *Transplantation*, **52**, 157-160.