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Switching From Tacrolimus to Cyclosporine A to Prevent Primary Biliary Cirrhosis Recurrence After Living-Donor Liver Transplantation

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Recurrence of primary biliary cirrhosis (PBC) after liver transplantation has been shown to negatively affect graft and patient survival. Recently, protective effects of cyclosporine A against PBC recurrence after liver transplantation have been reported. Participants were 4 patients who underwent living-donor liver transplantation (LDLT) for end-stage liver disease due to PBC. Tacrolimus was used for initial immunosuppression, and this was switched to cyclosporine A at least 3 months after liver transplantation. Targeted trough level of cyclosporine A was 20 times that of tacrolimus. We assessed liver and renal function, as well as antimitochondrial M2 antibody for recipients prior to LDLT, as well as before and after switching immunosuppressive agents. Patients were 1 man and 3 women, and they were ages 45 to 47 years at LDLT. Timing of switching from tacrolimus to cyclosporine A was 13, 3, 7, and 4 months respectively after liver transplantation, and all 4 patients have been on cyclosporine A without adverse effects at 20 to 46 months after transplantation. In 2 of 4 patients who had high titers of antimitochondrial M2 antibody before transplantation, antibody titer did not elevate after LDLT. In the other 2 patients without elevation of antimitochondrial M2 antibody, the titer did not turn positive. Switching from tacrolimus to cyclosporine A was possible without medical problems, and all patients exhibit no recurrence of PBC. Cyclosporine A may be useful for prevention of PBC recurrence after LDLT.

Key Words: Primary biliary cirrhosis – Living-donor liver transplantation – Immunosuppression – Recurrence

Primary biliary cirrhosis (PBC) has been one of the most common indications for liver transplantation in adults. Recurrence of PBC after liver transplantation has been shown to negatively affect graft and patient survival. Recently, protective effects of cyclosporine A (CyA) against PBC recurrence after liver transplantation have been reported.[1,2] Corticosteroids after liver transplantation may

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Table 1 Clinical variables before liver transplantation, and before and after switching from tacrolimus to cyclosporine A

	Patient 1			Patient 2			Patient 3			Patient 4		
	Pre-LT	Before	After	Pre-LT	Before	After	Pre-LT	Before	After	Pre-LT	Before	After
Anti-M2 antibody, U/mL	<5	<5	<5	<5	<5	<5	149	66	66	155	47	94
AST, U/mL	167	15	13	112	15	18	112	103	20	132	19	21
ALT, U/mL	51	9	6	78	9	8	43	163	15	83	22	15
Total bilirubin, mg/dL	12.0	0.8	0.6	2.2	0.4	0.3	19.6	2.1	0.9	19.0	0.6	0.6
Albumin, g/dL	2.8	3.8	4.5	3.0	3.3	3.9	2.7	3.5	4.0	2.3	3.7	4.1
PT-INR	1.2	1.0	1.0	1.2	1.0	1.0	1.2	1.0	1.0	1.2	1.0	1.0
Creatinine, mg/dL	0.4	0.74	0.76	0.48	0.65	0.78	0.5	0.62	1.02	0.68	1.19	1.37

ALT, alanine aminotransferase; AST, aspartate aminotransferase; pre-LT, before liver transplantation; PT-INR, prothrombin time–international normalized ratio.

be important to prevent recurrence of PBC.[3] We retrospectively assessed the outcome of switching from tacrolimus to CyA in patients who underwent living-donor liver transplantation (LDLT) for PBC.

Patients and Methods

Participants were 4 patients who underwent LDLT for end-stage liver disease due to PBC at Jikei University Hospital from 2008 to 2009. Tacrolimus and steroids were used for initial immunosuppression, and these were switched to CyA, steroids, and/or mycophenolate mofetil at least 3 months after liver transplantation. The targeted trough level of CyA was 20 times that of tacrolimus. We assessed liver function, renal function, antimitochondrial M2 antibody, and PBC recurrence among recipients before LDLT, and before and after switching immunosuppressive agents.

Results

Patient 1

The recipient was a woman age 45 years at LDLT who had received a diagnosis of PBC at age 36 years. The donor was the woman's 45-year-old husband. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the recipient's Model for End-Stage Liver Disease (MELD) score was 18, and her Child-Pugh score was 10. Immunosuppressive agent was switched from tacrolimus to CyA at 22 months after LDLT without medical problems or PBC recurrence (Table 1). Antimitochondrial M2 antibody remained negative after LDLT. After LDLT, the patient was treated with insulin for diabetes mellitus due to adverse effects of tacrolimus.

Patient 2

The recipient was a woman age 44 years at LDLT who had received a diagnosis of PBC at age 30 years. The donor was the woman's 48-year-old older brother. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the recipient's MELD score was 11, and her Child-Pugh score was 9. Immunosuppressive agent was switched from tacrolimus to CyA at 3 months after LDLT without medical problems or PBC recurrence (Table 1). Antimitochondrial M2 antibody remained negative after LDLT.

Patient 3

The recipient was a woman age 47 years at LDLT who had received a diagnosis of PBC at age 38 years. The donor was an 18-year-old daughter. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the MELD score was 20, and the Child-Pugh score was 10. Immunosuppressive agent was switched from tacrolimus to CyA at 7 months after LDLT. Recipient had a high titer of antimitochondrial M2 antibody before LDLT; antibody titer did not elevate after LDLT (Table 1). At 20 months after LDLT, liver biopsy was performed for liver dysfunction. Liver biopsy specimen revealed moderate late cellular rejection (isolated central perivenulitis) and mild acute cellular rejection [rejection activity index (RAI) = 2; P1 B1 V0] without PBC recurrence (Fig. 1A).

Patient 4

The recipient was a man age 46 years at LDLT who had received a diagnosis of PBC at age 43 years. The donor was the man's 43-year-old younger sister. ABO blood type–identical LDLT was performed

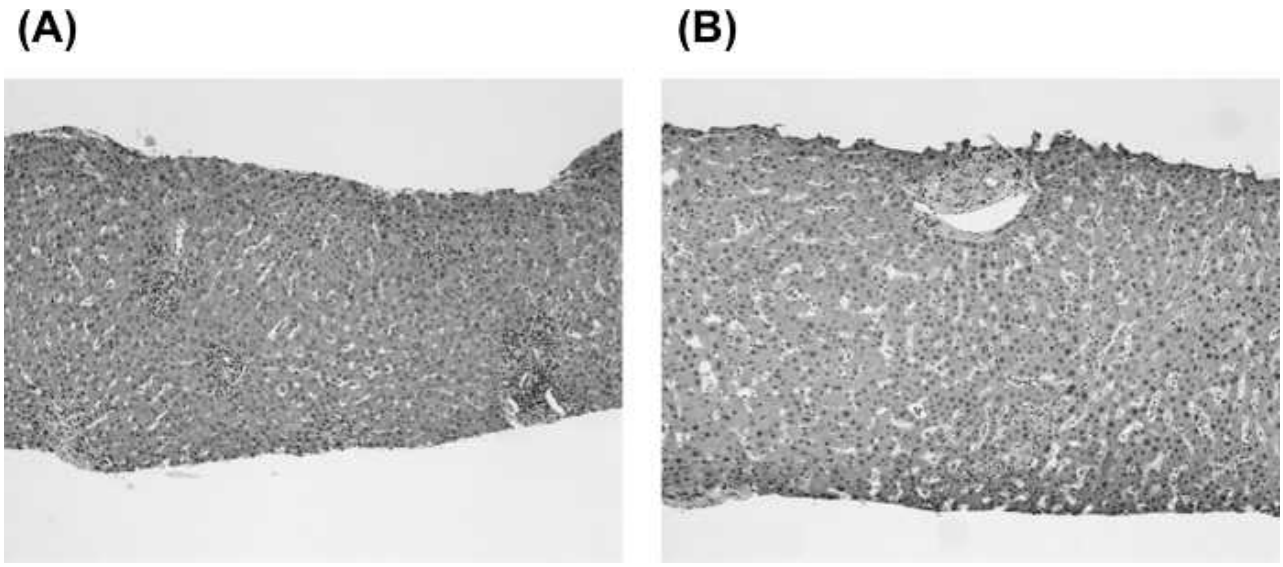

Fig. 1 (A) Liver biopsy specimen for liver dysfunction at 20 months after LDLT for patient 3 revealed moderate late cellular rejection (isolated central perivenulitis) and mild acute cellular rejection (RAI = 2; P1 B1 V0) without PBC recurrence. (B) Liver biopsy specimen for liver dysfunction at 8 months after LDLT for patient 4 revealed moderate acute cellular rejection (RAI = 4; P1 B2 V1) without PBC recurrence.

using the right lobe graft. At LDLT, the recipient's MELD score was 20, and his Child-Pugh score was 12. Immunosuppressive agent was switched from tacrolimus to CyA at 4 months after LDLT. Recipient had a high titer of antimitochondrial M2 antibody before LDLT; antibody titer did not elevate after LDLT (Table 1). At 8 months after LDLT, liver biopsy was performed for liver dysfunction. Liver biopsy specimen revealed moderate acute cellular rejection (RAI = 4; P1 B2 V1) without PBC recurrence (Fig. 1B).

Discussion

With the recent improvements in surgical, anesthetic, and microbiological techniques; the development of immunosuppressive agents; and increasing experience and better patient selection, better outcomes for liver transplantation for end-stage liver disease have been achieved. Liver transplantation is the treatment choice for patients with end-stage liver disease due to PBC; however, the incidence of recurrent PBC increases progressively, and histologic recurrent PBC is reported in approximately one third of patients by 10 years after liver transplantation.[1–6] The pathogenesis of PBC remains uncertain, and the perioperative clinical variables associated with recurrence of PBC after liver transplantation are not completely elucidated.

Despite the era effect of immunosuppressive agents, a major conclusion of most reports in patients who underwent liver transplantation for PBC is that the use of CyA is associated with a lower incidence of PBC recurrence in comparison with tacrolimus.[1–6] However, mechanisms of CyA for prevention of PBC recurrence are unknown. Conversely, tacrolimus is considered as a potent immunosuppressive agent with regard to mortality and graft loss at 1 year, as well as acute rejection.[7] Switching from tacrolimus as the primary immunosuppressive agent for PBC after liver transplantation to CyA as a maintenance immunosuppressive agent may enable safe prevention of PBC recurrence, as well as better outcomes.

Conclusions

Switching from tacrolimus to CyA was possible without sequelae, and all patients exhibit no recurrence of PBC. CyA may be useful for prevention of PBC recurrence after LDLT.

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