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Rituximab Induction to Prevent the Recurrence of PSC After Liver Transplantation—The Lessons Learned From ABO-Incompatible Living Donor Liver Transplantation

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Background. Multiple studies have failed to reveal an effective method for preventing the recurrence of primary sclerosing cholangitis (PSC) after liver transplantation (LTx). A national study conducted in Japan revealed several risk factors for the recurrence after living donor LTx (LDLTx); however, recipients of ABO-blood type incompatible (ABO-I) LTx were excluded from the previous analysis. In the present study, we investigated the efficacy of an immunosuppressive protocol in ABO-I LTx on the recurrence of PSC after LDLTx. **Methods.** We conducted a national survey and analyzed the outcome of recipients who underwent ABO-I LDLTx for PSC (n = 12) between 1994 and 2010 in 9 centers and compared the outcome with that of ABO-compatible LDLTx for PSC (n = 96). The key elements of the immunosuppressive regimen in ABO-I LTx are plasma exchange sessions to remove existing antibodies, and the use of immunosuppression to control humoral immunity. Rituximab was added to the immunosuppression regimen from 2006 onward; 5 patients received rituximab perioperatively. **Results.** All 7 recipients who underwent ABO-I LDLTx before 2006 (who did not receive rituximab) died of infection (n = 3), antibody-mediated rejection (n = 1), ABO-incompatibility associated cholangiopathy (n = 1) or recurrence of PSC (n = 2). In contrast, we found that all 5 recipients from 2006 (who were treated with rituximab) retained an excellent graft function for more than 7 years without any recurrence of PSC. **Conclusions.** The findings of this study shed light on the efficacy of a novel strategy to prevent the recurrence of PSC and the possible mechanisms provided by rituximab treatment are discussed.

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It is now known that the rate of primary sclerosing cholangitis (PSC) recurrence after liver transplantation (LTx) varies depending on risk factors and the length of

follow-up. Two recent large-scale studies from Germany (in 2015, 305 patients) and the United Kingdom (in 2015, 565 patients) reported that the rate of recurrence was 20.3% over a mean follow-up period of 8.4 years¹ and 14.3% over

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a median follow-up period of 9 years.² In 2011, Egawa et al³ (96 patients) demonstrated the specific risk factors associated with living donor LTx (LDLTx) in Japanese patients and noted that the overall recurrence rate was 27% over a median period of 3.5 years. These attempts to identify the risk factors for recurrence have thus far revealed that donation from first-degree relatives, an older donor age, a younger recipient age, inflammatory bowel disease (IBD) activity, a higher international normalized ratio of prothrombin time or a higher Model for End-Stage Liver Disease (MELD) score at the time of LTx, cytomegalovirus disease and early biliary complications are all potential risk factors.¹⁻⁴ In contrast, Aravinthan et al⁵ described relatively the favorable outcomes of LTx for PSC in cases involving donors from first-degree relatives; the study was performed at a single center, thus the findings should be confirmed by future studies. In any case, every effort should be made to avoid the above-mentioned risk factors. Although it was expected that preemptive colectomy might confer protective effects against disease recurrence in an early study from the United Kingdom,⁶ it was not firmly confirmed later on.

With the exception of a few Asian countries, ABO-incompatible (ABO-I) LTx is rarely performed. With the current desensitization protocol consisting of rituximab and plasma exchange, a case-matched comparison of ABO-I LTx and ABO-compatible (ABO-C) LTx showed almost equivalent patient survival over 3 years.⁷ Thus, ABO-I LTx is routinely performed in East Asia. The advantage of LDLTx over deceased donor LTx for PSC lies in the fact that the transplant can be scheduled before the recipient becomes too sick. The idea is based on the fact that a high MELD score is regarded as a risk factor for recurrence. However, the most common donors in LDLTx are first-degree relatives, such as the patient's father or mother, which is—unfortunately—another risk factor, and which represents a formidable dilemma.

In the present study of 5 PSC patients who underwent ABO-I LDLTx and who were treated with rituximab (median follow-up period, 7.2 years), the graft survival rate was 100% and there were no cases of recurrence. The demographic characteristics of these patients and possible protective mechanisms that may be provided by rituximab are discussed.

METHODS

Patient Selection and Data Collection

A nationwide survey was conducted in 29 centers; 132 patients were included. The demographic characteristics have been reported previously.³ Among these patients, 12 patients underwent ABO-I LDLTx for PSC in 9 centers between 1994 and 2010, and had been excluded from the previous analysis because of ABO-incompatibility. The following clinical and demographic data were retrospectively extracted from the database: transplant year, age, gender, blood type (donor and recipient), graft type, donor age, donor relationship to the recipient, the status of IBD, MELD score, immunosuppressive regimen, vascular and biliary complications, viral infection, episodes of rejection and the details of death. These parameters were compared with those of ABO-C recipients, which were collected in the previous nationwide study.³

The study was approved by the institutional ethical review board of Keio University School of Medicine (20170055).

The Diagnosis of Biliary Stricture and the Recurrence of PSC

If indicated by abnormal liver function tests, further investigations were carried out with biopsies and cholangiography by percutaneous transhepatic cholangiography or endoscopic cholangiography or magnetic resonance cholangiography. The diagnosis of recurrent PSC was made based on the criteria proposed by Graziadei et al,⁸ and the criteria that were used in the previous study.³ Biliary stricture in recipients of ABO-I LTx, which is presumably driven by antidonor blood type antibodies, almost exclusively occurs within 1 year after LTx^{9,10}; thus, the recurrence of PSC was considered to be the most likely diagnosis when patients presented with diffuse biliary stricture more than 1 year after LTx.

Data Analysis and Statistics

Fisher and χ^2 exact tests were used for the analysis of the categorical data. The *t* test and a nonparametric analysis were used to analyze noncategorical data. The statistical analyses of the categorical and noncategorical data were performed using the SPSS software program. Patient survival and recurrence free survival were evaluated using the Kaplan-Meier

TABLE 1.

The demographic characteristics of the ABO-I LDLTx recipients

Patient no.	LTx year	Age	Sex	Blood type (donor to recipient)	Graft	MELD	IBD	Donor (age)	Donor relationship
1	1994	23	M	B to O	ELLS	18	+	49	Mother
2	1999	26	F	B to A	Right	15	+	50	Mother
3	2001	31	M	A to O	Right	11	+	58	Father
4	2003	42	F	AB to O	Left	19	+	44	Spouse
5	2004	34	F	AB to B	Right	15	+	58	Mother
6	2005	46	M	AB to A	Right	20	+	48	Sister
7	2006	2	M	AB to B	LLS	11 ^a	–	35	Father
8	2006	6	M	A to O	ELLS	17 ^a	+	31	Aunt
9	2008	23	F	B to O	Left	15	–	30	Sister
10	2009	3	M	A to O	LLS	11 ^a	–	34	Mother
11	2010	54	F	A to O	Left	21	+	55	Spouse
12	2010	25	M	AB to B	Post	19	+	27	Sister

^a PELD score.

M, male; F, female; ELLS, extended left lateral segment; LLS, left lateral segment; Post, posterior segment; PELD, pediatric end-stage liver disease.

TABLE 2.
The pretransplant parameters of the ABO-C LTx and ABO-I LTx recipients

Characteristics	ABO-C (n = 96)	ABO-I (n = 12)	P
Age	33.79 ± 1.404	26.33 ± 4.579	0.1072
Sex	Male: 48, female: 48	Male: 7, female: 5	0.7709
MELD score	11.96	18	0.0313 ^a
IBD	With: 44, without: 49, unknown: 3	With: 9, without: 3	0.1227
Age (Donor)	44.92 ± 1.612	43.06 ± 3.266	0.7016
Sex (Donor)	Male: 58, female: 38	Male: 4, female: 8	> 0.9999
Gender mismatch	Match: 44, mismatch: 52	Match: 5, mismatch: 7	> 0.9999
Donor related or unrelated	Unrelated (siblings or spouse): 42; related (parents or son): 54	Unrelated: 6, related: 6	0.7629
Graft type	Left: 50, right: 43, lateral: 2, unknown: 1	Left: 7, right 4, right, lateral: 1	> 0.9999

^a Pediatric end-stage liver disease.

method and compared using the Log-rank test using the GraphPad Prism 6 software program (GraphPad Software, Inc., San Diego, CA). *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

Demographic Data

Between 1994 and 2010, 12 patients underwent ABO-I LDLTx for PSC. Ninety-six patients who underwent ABO-C LDLTx for PSC between 1994 and 2008 were also analyzed. Among the 12 patients, there were 3 male pediatric patients (2, 3, and 6 years of age) and 9 adult patients. The age of the adult patients ranged from 23 to 54 years (mean, 33.8 years). Five of the patients were female and 7 were male. The MELD score at the time of LTx ranged from 11 to 21 (mean = 18). The pediatric end-stage liver disease score of 3 pediatric patients were 11, 17, and 11. The other pretransplant parameters of the patients, including the blood type of the donor and recipients, the graft type, the IBD status, the donor age, the sex of the donor and the donor relationship are summarized in Table 1. None of the patients who underwent ABO-I LDLTx had undergone colectomy for IBD. The comparison

of the parameters with those of the ABO-C recipients, revealed that the MELD scores of the ABO-I recipients were significantly higher (*P* = 0.0313). None of the other parameters differed to a statistically significant extent (Table 2).

Desensitization

The desensitization protocols varied depending on the era. The protocols that each recipient received are shown in Table 3. The early protocol (before 2001) consisted of plasma exchange based on the antidonor blood type antibody titer and the performance of splenectomy at the time of LTx. After 2001, local infusion therapy, via either the portal vein (PV) or hepatic artery (HA), was added for patients (Pts) 3 to 6, and 8 to 11. The details of the local infusion therapy have been described elsewhere; briefly, prostaglandin E1, steroids with or without mesilate gabexiate were infused through a catheter placed in a branch of the PV or HA.¹¹ Rituximab was added to the immunosuppression (IS) regimen to improve desensitization from 2006 onward; 5 patients received rituximab perioperatively (Pts 8-12). The dosages of rituximab and the timings of administration are summarized in Table 3. IVIG was administered postoperatively to Pt 9 as prophylaxis

TABLE 3.
Desensitization, maintenance, and current IS

Patient no.	PE	Desensitization				Maintenance IS			
		Rituximab dosage and the timing ^a of administration	Local infusion	Splenectomy	IVIG	CNI	Antimetabolites	Steroid at 1POY	Current steroid dose
1	+	–	–	–	–	CyA	AZA ⇒ Cyclo	NA	NA
2	–	–	–	+	–	Tac	Cyclo	NA	NA
3	+	–	PV	+	–	Tac	AZA ⇒ Cyclo	+	NA
4	+	–	HA	–	–	Tac	Cyclo	NA	NA
5	+	–	HA	–	–	Tac	MMF	NA	NA
6	–	–	HA	–	–	Tac	MMF	+	NA
7	–	–	–	–	–	Tac	MMF	+	NA
8	–	375 mg/m ² , (–21)	PV	–	–	Tac	MMF ⇒ Miz	+	5 mg
9	+	500 mg (–14), 500 mg (–7)	PV	+	+	Tac	MMF	+	4 mg
10	+	375 mg/m ² , (–14)	PV	–	–	CyA	MMF	+	4 mg
11	+	500 mg, (–14)	PV	+	–	Tac	MMF	+	7.5 mg
12	+	500 mg, (–21)	–	+	–	CyA ⇒ Tac	MMF	+	1 mg

^a Days before the LDLTx.

CNI, calcineurin inhibitor; PE, plasma exchange; Tac, tacrolimus; CyA, cyclosporine A; AZA, azathioprine; MMF, mycophenolate mofetil; Cyclo, cyclophosphamide; Miz, mizoribine; NA, not applicable; POY, post-operative year.

TABLE 4.**The complications and outcomes after LTx**

Patient no.	Postoperative complications						Outcome	
	HAT	PVT	BD	ACR	AMR	CMV	Days post-LTx	Cause of death
1	–	–	–	+	–	–	Dead (27)	Infection
2	–	–	–	+	+	–	Dead (92)	AMR induced IHBD, Infection
3	–	+	–	–	–	+	Dead (1879)	Recurrence (1419 days)
4	–	–	–	–	–	+	Dead (144)	Infection
5	–	+	–	+	+	–	Dead (99)	Hepatic necrosis
6	+	–	+	–	–	+	Dead (2373)	Infection
7	–	–	–	+	–	+	Dead after Re-LTx (2555)	Recurrence (544 days)
8	–	–	–	–	–	–	Alive (3753)	–
9	–	–	–	–	–	+	Alive (3127)	–
10	+	–	–	+	–	+	Alive (2677)	–
11	–	–	–	–	–	+	Alive (2608)	–
12	–	–	–	–	–	+	Alive (2509)	–

HAT, hepatic artery thrombosis; PVT, portal vein thrombosis; BD, biliary duct complications; ACR, acute cellular rejection; CMV, cytomegalovirus infection; IHBD, intrahepatic biliary duct dilatation.

against antibody-mediated rejection (AMR). Splenectomy was performed in Pts 2, 3, 9, 11, and 12.

The Maintenance IS Protocol and the Current IS Regimen

The basic maintenance IS protocol for ABO-I LTx consisted of calcineurin inhibitors [either tacrolimus or cyclosporin A], steroids and antimetabolites. The current IS regimen of all survivors is also described in the Table 3. All of the patients who remained alive at 1 year post-LTx (Pts 3, 6–12) received varying doses of steroids. All of the recipients who remain alive at the time of writing (Pts 8–12) are on triple IS. The current steroid doses range from 1 to 7.5 mg.

The Overall Outcome and Recurrence

The postoperative complications are summarized in Table 4. All 7 patients who underwent transplantation before 2006 are dead. The causes of death were as follows: hepatic necrosis secondary to ABO AMR ($n = 1$), infection ($n = 4$), and hepatic graft failure due to the recurrence of PSC ($n = 2$). Recurrence was diagnosed based on the criteria described in Methods. Two patients were diagnosed with recurrent PSC at 1419 and 544 days after LTx, respectively. On the other hand, intrahepatic diffuse bile duct dilatation—presumably due to AMR—was observed in 1 patient (Pt 2) within 3 months after LTx. All 5 patients who received rituximab are alive at more than 7 years after transplantation (the median post-LTx survival is 2934 days) without any signs of recurrence. No statistical significance was observed in the incidence of postoperative complications in the ABO-I recipients who were treated with rituximab and the ABO-C recipients who were followed up for longer than 12 months (data not shown). Figure 1 shows the recurrence-free survival curves of the patients who underwent ABO-I LTx for PSC with and without rituximab (Figure 1A). Deaths due to early complications were censored. A log-rank test revealed that the recurrence-free survival of recipients who were treated with rituximab was significantly better in comparison to those who were treated without rituximab ($P = 0.0431$). The recurrence free survival of patients who underwent ABO-I LTx with rituximab ($n = 5$) did not differ from that of

patients who underwent ABO-C LTx ($n = 96$) ($P = 0.0519$) (Figure 1B).

DISCUSSION

The criteria suggested by Graziadei et al in 1999 to diagnose the recurrence of PSC consists of an established diagnosis of PSC before LTx and cholangiographic or histological

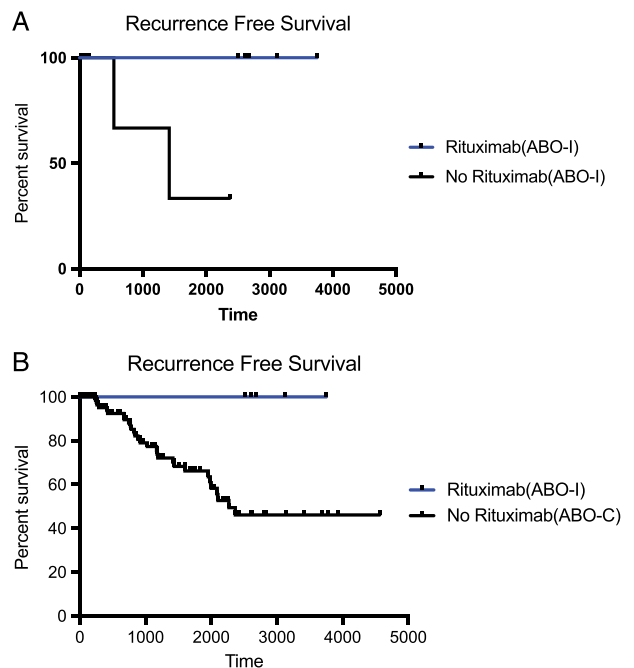


FIGURE 1. A, Kaplan-Meier curves of the recurrence-free survival rates of patients who underwent ABO-I LTx with rituximab ($n = 5$) and without rituximab ($n = 7$). A log-rank test revealed that the recurrence-free survival rate of recipients who were treated with rituximab was significantly better than that of patients who underwent ABO-I LTx without rituximab ($P = 0.0431$). B, The Kaplan-Meier curves of the recurrence-free survival rates of patients who underwent ABO-I LTx with rituximab and the patients who underwent ABO-C LTx. The recurrence free survival rate of the patients who underwent ABO-I LTx with rituximab treatment ($n = 5$) and that of the patients who underwent ABO-C LTx ($n = 96$) did not differ to a statistically significant extent ($P = 0.0519$).

evidence of PSC after LTx; however, the criteria excluded HA thrombosis, ductopenic rejection and ABO incompatibility. In Japan, due to the scarcity of deceased donors and recent progress in long-term graft survival, ABO-I LDLTx are routinely performed. The advances in graft survival in ABO-I LTx recipients primarily depend on the advent of rituximab. Recent large-scale studies of ABO-I LTx in patients who received the updated protocol, reported high success rates.^{7,9,12-14} A Japanese nationwide survey revealed that the only risk factor for AMR was the absence of rituximab,¹⁰ and that the 3-year survival rate increased from 30% to 80% after the introduction of rituximab.¹⁵ However, diffuse intrahepatic biliary stricture is still a concern, presumably due to the immunological responses to ABO-blood type antigen on biliary epithelial cells (BECs). Thus, patients who underwent ABO-I LTx were excluded from the previous nationwide study on LTx for PSC to avoid confounding factors. In this study, 12 Japanese patients who underwent ABO-I LDLTx for PSC between 1994 and 2010 were analyzed. Recurrence was observed in 2 cases, at 1419 and 544 days after LTx, respectively. The diagnosis of recurrence was favored since biliary stricture due to ABO blood type antibodies almost always occurs within 1 year after LTx.⁹ There was 1 case of intrahepatic biliary dilatation in a patient who underwent LTx without rituximab (Pt 2). A diagnosis of cholangiopathy associated with ABO-blood type incompatibility was favored in this case based on the timing (within 3 months after LTx) and the preceding episode of AMR. In short, recurrence was observed in 2 of 3 patients who achieved long-term survival in

an ABO incompatible setting before the rituximab-era, despite the provision of intensive IS (ie, splenectomy, IVIG, local infusion).

Most importantly, the transplanted liver retained an excellent graft function in all 5 patients who received rituximab induction after 2006, without any signs of recurrence. With the exception of mild portal fibrosis, histological examinations revealed no characteristic findings of recurrent PSC in any of the 5 surviving patients.¹⁶ Due to the insufficient number of patients, the difference in the recurrence-free survival of the ABO-I LTx patients who were treated with rituximab did not differ from that of the ABO-C LTx patients. However, this observation led us to hypothesize that B cell depletion by rituximab might prevent the recurrence of PSC. Early clinical trials to assess the efficacy of other immunosuppressive-based therapies on the course of PSC, such as steroids, azathioprine, cyclosporin A, tacrolimus, methotrexate and mycophenolate mofetil, have failed to identify any clinical benefits, which seems to be compatible with the fact that PSC can recur after LTx in patients receiving IS with these drugs.¹⁷ However, with the exception of a pilot study, no studies have investigated the effects of rituximab on PSC,¹⁸ and there have been no registered therapeutic trials utilizing rituximab for preventing the recurrence of PSC after LTx.

Thus far, the mechanism underlying the prevention of recurrence by rituximab remains to be elucidated; however, it seems reasonable to investigate autoantibodies and B cells producing autoantibodies. The similarity of biliary stricture observed after ABO-I LTx also indicates a common pathogenesis

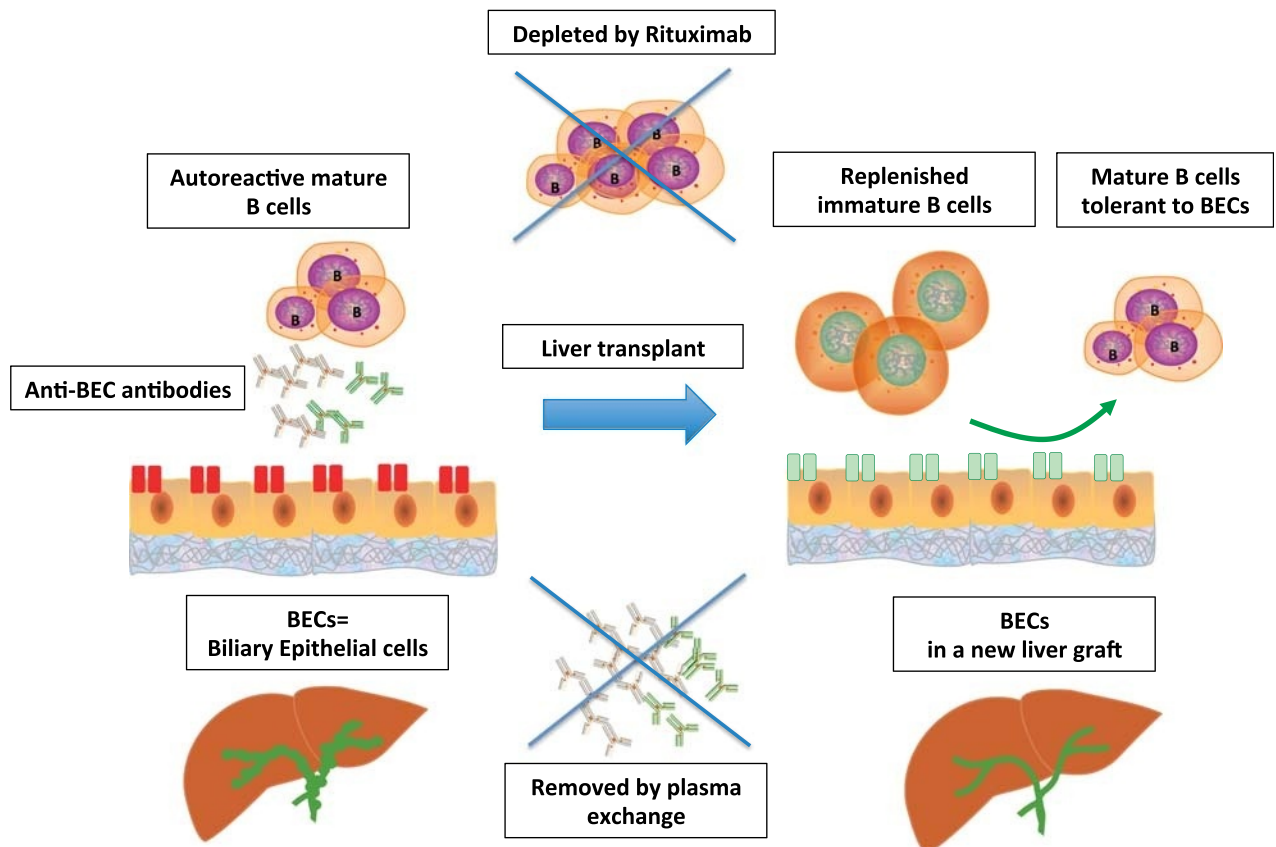


FIGURE 2. The hypothesized mechanism by which PSC recurrence is prevented after LTx. Autoantibodies against BECs were removed by the PE sessions. Autoreactive B cells against BECs are abrogated by rituximab and newly replenished immature B cells are tolerized when they encounter the new liver allograft in the presence of IS.

with cholangiopathy in PSC patients. Several studies have suggested candidate autoantibodies, such as antineutrophil cytoplasmic antibody, antinuclear antibody, and antismooth muscle antibody; however, their disease specificity is quite low and their significance is unclear.¹⁹ An interesting study conducted by Sumitran-Holgersson et al²⁰ reported that anti-BEC autoantibodies were frequently observed in patients with PSC. A subsequent study by the same group provided insights into the mechanism linking the presence of anti-BEC antibodies and the pathogenesis of PSC.²¹ One hypothesis is that autoreactive B cells targeting BECs produce autoantibodies and provide signals for the immune system, which subsequently attacks the biliary tree. This hypothesis is corroborated by growing evidence to support the efficacy of rituximab in inducing and maintaining the remission of autoantibody-mediated cholangiopathy in patients with IgG4-related cholangiopathy.²² Based on these observations, the removal of existing autoantibodies by plasma exchange sessions, the depletion of autoreactive B cells and the induction of tolerance to such B cells by rituximab may—in theory—prevent PSC after LTx (Figure 2). However, how does rituximab help induce tolerance to autoreactive B cells? It is now well known that antidonor blood type antibody titers are well suppressed after successful ABO-I LTx, in comparison to before transplantation, when patients are treated with rituximab.^{10,14,15} One possible explanation for this finding is that rituximab depletes memory B cells and that the process of receiving a liver graft expressing the ABO antigen in the presence of IS induces tolerance to replenishing immature B cells that are capable of producing ABO-blood type antibodies. It is also possible that a similar induction of tolerance can occur in B cells targeting BECs.

The present study is associated with several limitations. This study was an uncontrolled retrospective study and the study population was relatively small. ABO-I LTx with rituximab was conducted in a newer treatment era (2006–2010), while the patients in the control group who underwent ABO-C LTx were treated between 1994 and 2008. However, it is important to note that as the time to recurrence in the ABO-C LTx recipients ranged from 8 to 79 months after LDLTx, the survival period of all ABO-I LDLTx recipients who received rituximab exceeded this observation period.

In conclusion, rituximab induction therapy could be the promising novel treatment to prevent the recurrence of PSC after LTx. We hope that our preliminary data could lead to a larger study from multiple Asian centers, which will elucidate the efficacy of rituximab and the mechanism of B cell depletion upon the prevention of recurrence after LTx in PSC patients.

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