OPEN

Rituximab Desensitization in Liver Transplant Recipients With Preformed Donor-specific HLA Antibodies: A Japanese Nationwide Survey

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Background. The significance of preformed donor-specific anti-HLA antibodies (DSAs) in liver transplant recipients is controversial. Moreover, there has been no established desensitization protocol for DSA-positive recipients. **Methods.** A Japanese nationwide survey was performed to investigate the clinical practice among preformed DSA-positive patients with special reference to rituximab desensitization. **Results.** There was a total of 47 cases, including 2 pediatric cases, in which rituximab (287 ± 159 mg [319 (50–916)/m^2]) was administered to desensitize preformed DSA. The decision for the indication of rituximab desensitization was based on a single-antigen assay in the majority of cases (83%, 39/47), and the most frequent protocol was rituximab monotherapy (n = 12) followed by quadruple treatment with rituximab tacrolimus, mycophenolate mofetil, and plasmapheresis (n = 11). The overall 1-, 3-, and 5-y graft and patient survival rates among adult patients were 85%, 83%, 83%, and 81%, 77%, 74%, respectively, while neither graft loss nor death was observed in the 2 pediatric cases. The 1-, 3-, and 12-mo cumulative incidence of antibody-mediated rejection (AMR) was 11%, 13%, and 13%, respectively. The incidence of AMR was significantly higher in the lower rituximab dose group than in the higher rituximab dose group (cutoff 300 mg/m^2, 4% versus 24%, $P = 0.041$). The rate of infusion-related adverse drug reactions (ADRs) was 4.4%, and all ADRs were mild and self-limiting. A total of 99 ADRs among 27 patients were reported, none of which were severe adverse events associated with rituximab. **Conclusions.** The rituximab induction was well tolerated among DSA-positive liver transplant recipients with a satisfactory outcome. A rituximab dose >300 mg/m^2 was observed to achieve less incidence of the development of AMR.

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INTRODUCTION

Preformed donor-specific anti-HLA antibody (DSA) is associated with poor graft survival after kidney, pancreas, or heart transplantation, mainly due to an increased risk of acute or chronic antibody-mediated rejection (AMR).[1,2] In kidney transplantation, risk-stratification on the basis of preformed DSA is now possible due to the availability of detection assays, and an association between DSA and increased risk of graft failure has been confirmed, for which induction therapy using polyclonal antibodies with or without rituximab is established.[3,4] In contrast, the liver had been considered an immunologically privileged organ, and the effect of preformed DSA or de novo DSA after liver transplantation (LT) has remained controversial.[5] Recent studies suggest that high levels of preformed DSA and de novo DSA can induce early graft rejection, accelerate liver fibrosis, and even accelerate early graft failure, leading to impaired graft and patient survival.[6,7] Therefore, physicians should be aware of the possible effects of preformed DSA on patient outcome after LT and establish an immunologic strategy for DSA to prevent potential detrimental effects.

In Japan, where living donor LT (LDLT) is the mainstay for LT, positive lymphocyte complement-dependent cytotoxic

crossmatching (CDCXM) is often encountered preoperatively, and immunologic management for such cases has long been debated.[8-10] In addition, the safety and efficacy of rituximab desensitization for ABO blood-type incompatible LDLT has evolved and is established in Japan.[11] Accordingly, rituximab desensitization for liver transplant recipients with preformed DSA coupled with or without crossmatching positivity has been performed in several leading Japanese transplant centers.

The aim of the present study was to review the current state-of-the-art rituximab-based desensitization protocols used in liver transplant recipients with preformed DSA in Japan, and to simultaneously ascertain the safely profile of intravenous rituximab as an induction therapy among DSA-positive liver transplant recipients.

PATIENTS AND METHODS

Data Collection

In collaboration with the Japan Society for Transplantation and the Japanese Liver Transplant Society, questionnaires regarding LT for patients with preformed DSA were sent to registered 51 liver transplant centers having performed LT between 2001 and 2016. Among those, 14 centers had experience with LT in cases with preformed DSA, and additional questionnaires were completed about the desensitization for preformed DSA, with detailed data collection. Finally, liver transplant recipients with preformed DSA who were administered rituximab for desensitization were the subjects of the present study. The collected information included age, sex, disease, recipient and donor blood types, Model for End-Stage Liver Disease score, transplant type, graft type, assays for the detection of preformed DSA, and the corresponding results. Treatment data included graft size, splenectomy, desensitization protocol other than rituximab, timing and dose of rituximab, and all morbidities that were recorded as adverse events. Clinical data included preoperative and post-operative DSA results, if available, as well as AMR; acute cellular rejection; serious or nonserious adverse events; and adverse drug reactions (ADRs), including bacterial infection, fungal infection, cytomegalovirus (CMV) antigenemia; and patient survival. Data on mortality and cause of death were also collected.

Detection of the Presence of Preformed DSA

Several techniques were used to detect the presence of donor-specific HLA immunoglobulin antibodies: T-cell and B-cell CDCXM, T-cell and B-cell flow cytometric crossmatching (FCXM), immunocomplex capture fluorescence analysis (ICFA) for class I and class II, panel reactive antibody (PRA) assay for class I and class II antigens, and single-antigen assay for class I and class II. All tests and HLA typing were performed by HLA specialists at each center in accordance with the test manufacturer's instructions. The maximal value of median fluorescent intensity (MFI) by Luminex methods (ICFA, PRA, and single antigen) of DSA for HLA A/B/DR/DQ was recorded, the cutoff values for which were center-dependent.

Rituximab-based Desensitization Protocol

Because the administration of rituximab for desensitization of preformed DSA is off-label use in Japan as well as in other countries, the desensitization protocols were center-dependent, and were approved by the institutional review board or ethics committee of each institution.

Definitions

Liver biopsies were performed when liver enzyme levels were increased. All rejection episodes, including cellular and antibody-mediated, were confirmed by biopsy and classified according to the Banff classification.[12] Immunohistochemistry for complement component 4d staining was performed in formalin-fixed, paraffin-embedded sections. Diffuse complement component 4d staining (>50%) of the portal microvasculature was considered positive. The acute AMR score was calculated as previously described by O'Leary et al.[13] In addition, acute AMR was diagnosed according to the clinical findings of hepatic necrosis and refractory intrahepatic biliary cholangitis, as described previously.[14] Safety was assessed by monitoring and recording all ADRs and serious ADRs occurring during and after rituximab treatment, including abnormalities that were identified from laboratory evaluations, vital sign measurement, and physical examination. ADRs were coded according to the Japanese version of the ICH Medical Dictionary for Regulatory Activities (MedDRA/J) and graded using the Common Terminology Criteria for Adverse Events version 4.0 (Japan Clinical Oncology Group). Infectious diseases were defined as infections with known pathogens requiring treatment.

Statistical Analyses

Continuous variables are expressed as means and standard deviations or as medians and ranges. Categorical and continuous data were compared between groups using the chi-square or Fisher exact and Student *t* or Mann-Whitney U tests, respectively, as appropriate. Overall survival and development of rejection and infectious diseases were estimated with the Kaplan-Meier method and compared with the log-rank test. Statistical analyses were performed using Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, version 23.0; IBM Corp, Armonk, NY) or SAS software version 9.4 (SAS Institute Inc, Cary, NC). A *P* value of <0.05 was considered statistically significant. The study was approved by the ethics committees of the institutions at which the survey was conducted (approval number at Ichikawa General Hospital Tokyo Dental College: I 16-63).

RESULTS

Patient Demographics

A total of 7435 liver transplants were performed in Japan from 2001 to 2016. Among a total of 135 DSA-positive cases (1.8%), 48 (0.6%), including 2 pediatric cases, received intravenous rituximab for desensitization of preformed DSA. Data were not obtained for 1 adult patient, and thus the subjects of the present study were 47 cases, including 2 pediatric cases. The median number of cases per center was 4 (1–11). Seven centers experienced only 1 case. The demographics of these 47 recipients and corresponding donors are presented in Table 1. The recipients were 7 male and 40 female individuals with a median age at transplantation of 45 (19–67) y in adults and 0 or 3 y in the 2 children. The most frequent cause of liver disease was hepatitis C virus cirrhosis (n = 13), followed by primary biliary cholangitis (n = 12), alcoholic cirrhosis (n = 6), hepatitis fulminant (n = 4), hepatic cirrhosis (n = 4), biliary

TABLE 1.

Patient demographics

	Adult (N = 45)	Pediatric (N = 2)
Age (y)	45 (0–67)	0, 3
Gender (M/F)	6/29	1/1
CPT classification (A/B/C)	1/8/36	0/1/1
MELD or PELD score	18 (4–36)	14, 29
Donor age	39 (19–69)	34, 36
Donor (deceased/living)	9/36	0/2
Graft type (whole/right/left/left lateral)	9/15/21/0	0/0/1/1
Graft to recipient weight ratio	1.05 (0.64–3.39)	2.48, 2.62
Blood type (match/compatible/incompatible)	23/10/12	1/0/1

CPT, Child-Pugh-Turcotte; MELD, Model for End-Stage Liver Disease; PELD, pediatric end-stage liver disease.

atresia (n = 2), autoimmune hepatitis (n = 1), Budd-Chiari syndrome (n = 1), idiopathic portal hypertension (n = 1), hepatitis B cirrhosis (n = 1), primary sclerosing cholangitis (n = 1), and Alagille syndrome (n = 1). Coexistence of hepatocellular carcinoma was observed in 3 cases. All LTs with rituximab desensitization were performed between 2009 and 2016, and the median follow-up period of this cohort was 40 (0.3–96) mo.

Screening for DSA

A summary of the histocompatibility tests performed and the results before transplantation are shown in Table 2. T-CDCXM and B-CDCXM were performed in 29 cases (62%) with a 45% (13/29) positive rate and 18 cases (38%) with a 67% (12/18) positive rate, respectively. T-FCXM was performed for 27 cases with a 74% (20/27) positive rate, and B-FCXM was performed for 19 cases with a 79% (15/19) positive rate. ICFA class I and class II were examined in only 1 case, and the result was negative for both. PRA class I and class II were examined for 13 cases with 100% and 77% (10/13) positive rates, respectively. Single-antigen class I and class II were assessed in 31 cases with a 97% (30/31) positive rate and 33 cases with a 70% (23/33) positive rate, respectively. Confirmation of the presence of preformed DSA and the decision for the indication of rituximab desensitization were based on a single-antigen assay in the majority of cases (83%, 39/47) and on PRA in 7 cases (15%), while positive CDCXM was the only basis for the rituximab desensitization for DSA in 1 case.

TABLE 2.

The results of screening tests for DSA

Screening assays	N	Positive results rate	Cutoff
CDCXM			
T-CDCXM	29	45%	1%–20%
B-CDCXM	18	67%	1%–30%
FCXM			
T-FCXM	27	74%	1.3–1.5
B-FCXM	23	70%	1.3–1.7
ICFA			
Class I	1	0%	Index >2.0
Class II	1	0%	Index >2.0
PRA assay			
Class I	13	100%	Positive cell
Class II	13	77%	Positive cell
Single-antigen assay			
Class I	31	97%	MFI 500–1000
Class II	33	70%	MFI 500–1000

CDCXM, complement-dependent cytotoxic crossmatching; FCXM, flow cytometric crossmatching; ICFA, immunocomplex capture fluorescence analysis; MFI, median fluorescent intensity; PRA, panel reactive antibody.

Administration of Rituximab and Other Desensitization Treatments

In principle, rituximab was administered preoperatively in 43 cases in which the presence of DSA was confirmed during the pretransplantation workup. The median number of s from rituximab administration to LT was 14 (0–85) d. In contrast, 4 patients whose DSA was confirmed postoperatively received rituximab on postoperative d(POD) 1 (0–4) after LT. Two patients underwent rituximab desensitization, both just before and just after the transplantation. The cumulative dose of rituximab was 287 ± 159 mg (319 [50–916])/m^2; 500 mg/body in 20 cases (7 centers), 300 mg/body in 16 cases (4 centers), 375 mg/m^2 in 5 cases (2 center), 50 mg/m^2 in 5 cases (1 center), and 100 mg/m^2 in 1 case (1 center). Tacrolimus was administered pretransplantation in 20 patients, starting 7 (0–36) d before transplantation. Mycophenolate mofetil was started preoperatively in 30 patients at 7 (0–26) d before transplantation. Additional IVIG and mizoribine for desensitization were used in 1 case each. Preoperative plasmapheresis was performed 2 (1–10) times in 26 cases. The desensitization protocol among this cohort is summarized in Table 3. The most frequent protocol was rituximab monotherapy (n = 12) followed by quadruple treatment with rituximab tacrolimus, mycophenolate mofetil, and plasmapheresis (n = 11). Splenectomy was performed intraoperatively in 16 cases; however, this was not for desensitization but for the modulation of portal flow and the facilitation of antiviral treatment using interferon in hepatitis C patients.

For the prevention of infusion reactions to rituximab, ascribed to either anaphylaxis or allergic reactions, either or both acetaminophen (17 patients, 36%) and intravenous antihistamine (42 patients, 89%) as well as steroids (35 patients, 74%) were administered before the administration of intravenous rituximab.

TABLE 3.

Rituximab-based desensitization protocol

Protocol	N	Number of centers
Rituximab monotherapy	12	4
Dual (N = 3)		
Rituximab + MMF	1	1
Rituximab + PE	2	2
Triple (N = 12)		
Rituximab + Tac + MMF	6	1
Rituximab + MMF + PE	5	1
Rituximab + IVIG + PE	1	1
Quadruple (N = 17)		
Rituximab + Tac + MMF + PE	11	3
Rituximab + MMF + MP + PE	5	1
Rituximab + Tac + Mizoribine + MP	1	1
Quintuple (N = 2)		
Rituximab + Tac + MMF + MP + PE	2	1
Sextuple (N = 1)		
Rituximab + Tac + MMF + MP + IVIG + PE	1	1

MMF, mycophenolate mofetil; MP, methylprednisolone; PE, plasma exchange; Tac, tacrolimus.

Chronologic Change in MFI in a Single-antigen Assay and CD-20⁺ Cells

Preoperative MFI for class I and class II DSAs was available in 27 cases and 22 cases, respectively, with median values of 5706 (1045–23 535) and 12 280 (8–22 734), respectively. The preoperative MFI and the posttransplant MFI after rituximab-based desensitization are shown in Figure 1. In addition, the frequency of CD-20⁺ cells, recorded in 24 patients, is shown in Figure 2, in which an abrupt decrease immediately after the administration of rituximab is confirmed. The recovery of CD-20⁺ cells was seen at 12 mo after LDLT.

Patient Outcome

Overall 1-, 3-, and 5-y graft and patient survival rates among the 45 adult patients were 85%, 83%, and 83%, and 81%, 77%, and 74%, respectively. Ten deaths occurred from infection (n = 5), graft failure (n = 4), and respiratory failure (n = 1). Neither graft loss nor death occurred in the 2 pediatric cases. The development of AMR was observed in 6 patients (13%) diagnosed on POD 12 (7–34). The 1-, 3-, and 12-mo cumulative incidence of AMR was 11%, 13%, and 13%, respectively. Three of these patients were lost: 2 patients due to graft loss for AMR on POD 70 and 542, respectively, and 1 due to respiratory failure on POD 21. Acute cellular rejection was observed in 12 cases (26%) diagnosed on POD 89 (6–1374). There was only 1 patient who developed both AMR and acute cellular rejection. The incidence of all infectious complications and CMV infection (including positive antigenemia) among the entire cohort was 47% (22/47) and 36% (17/47), respectively.

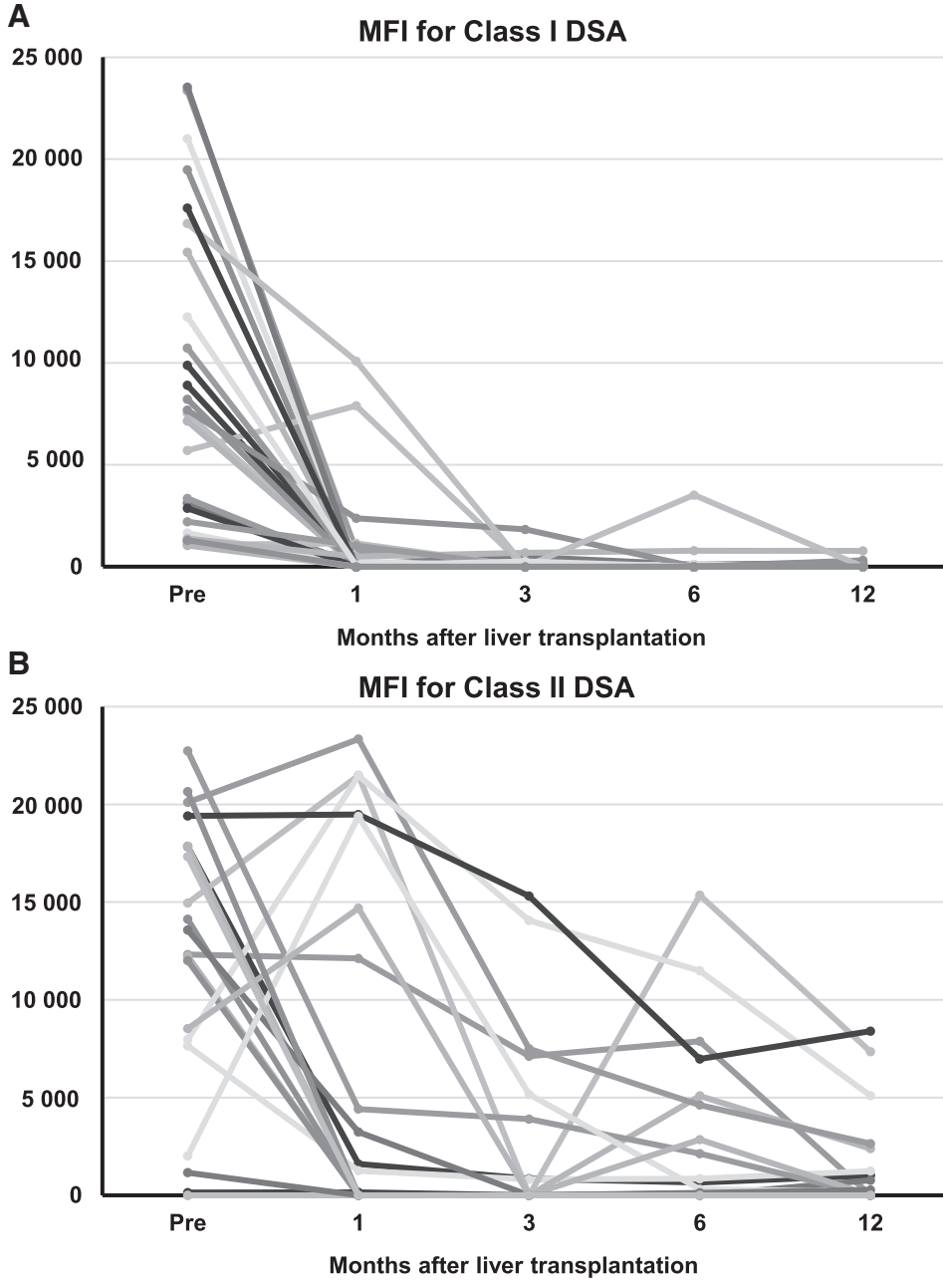

FIGURE 1. Chronologic change in the median fluorescent intensity in single antigen assays for HLA class I DSA (A) and HLA class II DSA (B). DSA, donor-specific antibody; MFI, median fluorescent intensity.

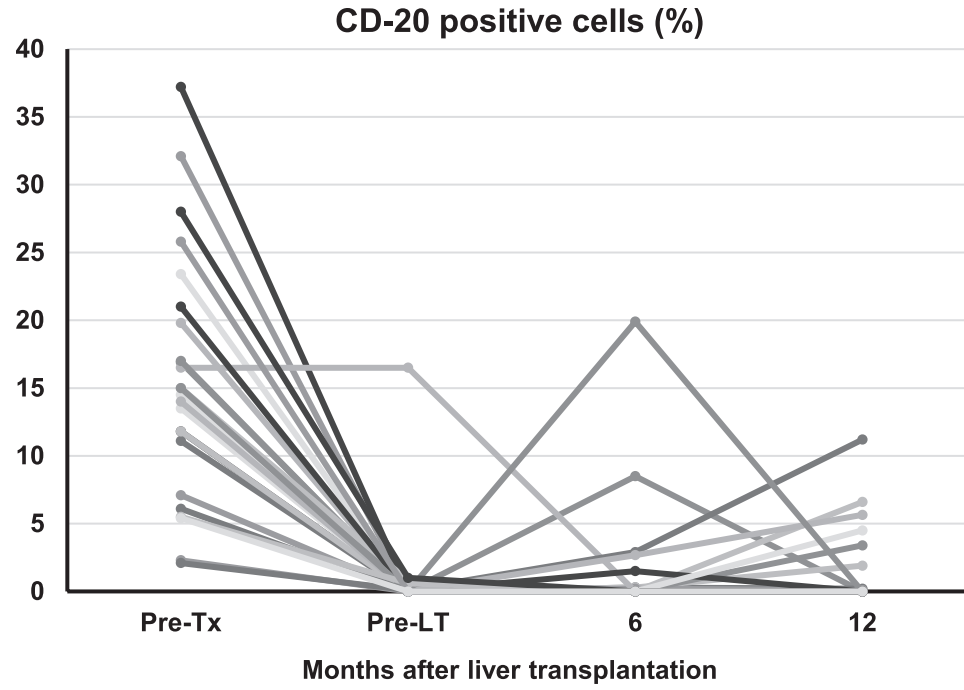

FIGURE 2. Chronologic change in the frequency of CD-20-positive cells. Pre-LT, just before liver transplantation; Pre-Tx, before administration of rituximab.

When the patients were divided by the cumulative dose of rituximab (≥300 versus <300 mg/m^2), the groups did not differ significantly in the development of acute cellular rejection (23% versus 29%, $P = 0.67$), infectious complications (46% versus 33%, $P = 0.37$), or CMV infection (35% versus 38%, $P = 0.81$), but the incidence of AMR was significantly higher in the lower dose group than in the higher dose group (4% versus 24%, $P = 0.041$; Figure 3).

Safety

A total of 27 adult patients (60%, 27/45 cases) experienced some kind of ADR (n = 99) during hospitalization for LT, the majority of which were mainly attributed to the LT itself. No adverse events were reported in the 2 pediatric patients.

Intravenous rituximab infusions were generally well tolerated; 2 adult patients (4.4%, 2/45 cases) experienced

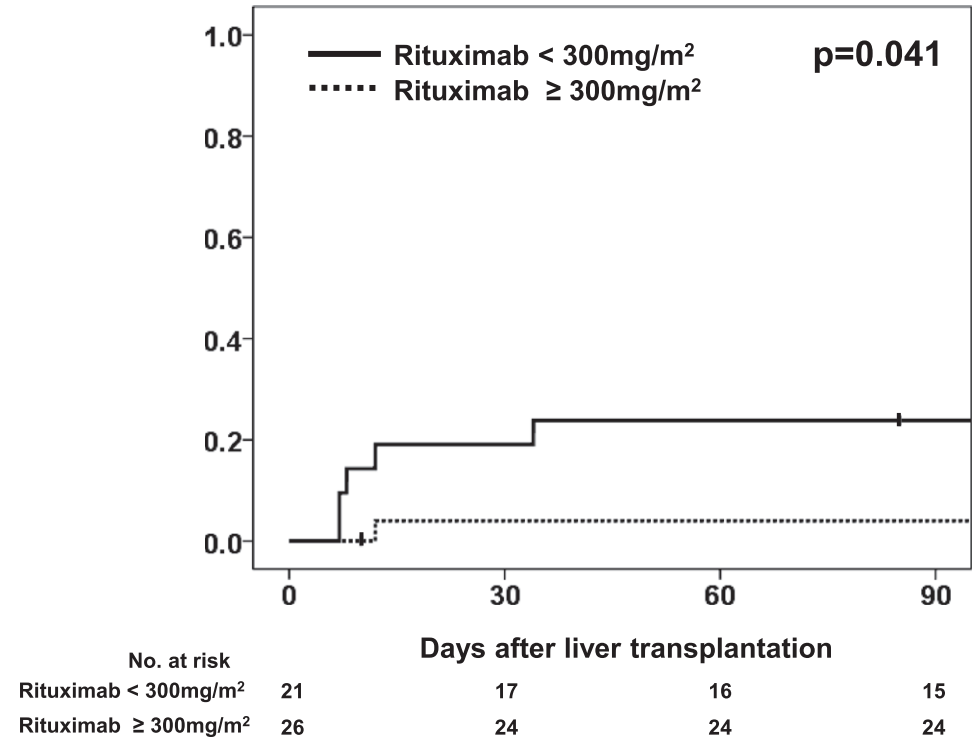

FIGURE 3. Incidence of antibody-mediated rejection stratified by the rituximab dose.

infusion-related ADRs: fever (n = 2), transient hypotension, and hot flash, all of which were mild (grade 1) and self-limiting.

During the pretransplantation period, there were 20 ADRs in 10 patients; the above-described infusion reactions (n = 4), thrombocytopenia (n = 4), leukocytopenia (n = 2), renal impairment (n = 2), liver enzyme elevation (n = 2), CMV antigenemia (n = 1), serum bilirubin elevation (n = 1), serum lactate dehydrogenase evaluation (n = 1), postprocedural hemorrhage (n = 1), anemia (n = 1), and lower extremity edema (n = 1). Among those, 6 ADRs were associated with rituximab, 8 were unrelated, and 6 were with unknown relation. Grade 3 or higher ADRs were postprocedural hemorrhage (n = 1, grade 4), thrombocytopenia (n = 3, grade 3), increased serum bilirubin level (n = 1, grade 3), liver enzyme elevation (n = 2, grade 3), lower extremity edema (n = 1, grade 3), and anemia (n = 1, grade 3).

A total of 79 posttransplantation ADRs occurred in 24 patients, among which 5 events were related, 51 events were with unknown relation to rituximab administration, and 23 events were unrelated. No severe ADR was diagnosed as related to rituximab administration. Grade 3 or higher ADRs, all of which were with unknown relation or without relation to rituximab, were catheter infection (n = 1, grade 5), sepsis (n = 1, grade 5), respiratory failure (n = 1, grade 4), pulmonary edema (n = 1, grade 4), neutropenia (n = 2, grade 3 and grade 4), leukocytopenia (n = 2, grade 3 and grade 4), hepatitis C (n = 1, grade 3), pneumocystis jirovecii pneumonia (n = 1, grade 3), bacterial pneumonia (n = 2, grade 3), urinary tract infection (n = 5, grade 3), peritonitis (grade 3, n = 1), acute cholangitis (n = 1, grade 3), and biliary anastomotic complication (n = 1, grade 3). The posttransplantation ADRs are summarized in Table 4.

TABLE 4.

Summary of postoperative adverse drug reactions

	N = 79	Grade
Related		
CMV infection	2	2
CMV antigenemia	2	1–2
Fungal infection	1	2
Unknown relation		
Infectious event		
Sepsis	1	5
Invasive fungal infection	1	2
Bacterial pneumonia	3	2–3
Urinary tract infection	6	1–3
Pneumocystis jirovecii pneumonia	1	3
CMV infection	2	2
CMV antigenemia	13	1–2
Recurrent viral hepatitis	2	2–3
Herpes virus infection	3	2
Peritonitis	1	3
Cholangitis	1	3
Catheter infection	1	5
Leukocytopenia (neutropenia)	7	2–4
Pulmonary edema	1	4
Respiratory failure	1	4
Biliary complication	1	3
Thrombotic microangiopathy	1	2
Toxic encephalopathy	1	2
Rejection	1	2
Fever	3	1–2
Unrelated		
Infectious event		
Sepsis	1	5
Invasive fungal infection	1	5
Bleeding	3	5
Respiratory failure	1	5
Anemia	3	2–3
Recurrent viral hepatitis	3	2–4
Fever	1	1
Diarrhea	2	3–4
Pleural effusion	2	2
Rejection	2	2
Hypertension	1	2
Hypotension	1	2
Hepatic encephalopathy	1	2
Arthralgia	1	2

CMV, cytomegalovirus.

DISCUSSION

In the present study, we described the rituximab-based desensitization protocol and its safety among liver transplant recipients with preformed DSA. Intravenous rituximab induction was well tolerated without relevant severe adverse events among liver transplant recipients, and the 5-y graft survival rate of 87% among the cohort seems acceptable.

Approximately 20% of liver transplant recipients have preformed DSAs at the time of transplantation, but the majority of recipients with preformed DSA show a rapid decrease in DSA postoperatively and persistent DSA negativity thereafter.[15-17] This phenomenon is likely a result of the unique ability of the liver to absorb DSA, thereby preventing the initiation of catastrophic injury in the majority of cases, which may make the liver an immunologically privileged organ.[18] Nevertheless, several recent studies reported that the presence of preformed DSA could affect graft and recipient outcomes in deceased donor LT (DDLT). In 2008, a study with a cohort of 896 Spanish liver transplant recipients demonstrated an association between DSA and 1-y graft survival.[19] In 2013, O'Leary et al[20] found that both preformed class I and II DSA MFI >5000 were significantly associated with a higher rejection rate and impaired patient survival among 1270 US liver transplant recipients. In the same study, they suggested the possible protective effect of daclizumab induction against the development of rejection among DSA-positive recipients. In 2016, McCaughan et al[21] reported among 459 Scottish liver transplant recipients that DSA with MFI ≥10 000 was significantly associated with a 1-y patient survival. In contrast, more recently, in 2019, Del Bello et al[22] found among 1788 French liver transplant recipients that preformed DSA with a high MFI was not associated with patient outcome, while an increased risk of acute rejection was confirmed in those with high-MFI DSA. In the same study, the use of rituximab as an induction therapy neither reduced the risk of acute rejection nor affected patient outcome. Regarding LDLT, in a study of 616 Japanese LDLTs, preformed HLA class I DSA with MFI >10 000 had a significant negative effect on the patient outcome.[23] Conflicting reports were recently published from Korean[24] and Japanese[25] centers, with the Korean group finding no effect of preformed DSA on the outcome, and the Japanese group finding a significant effect of preformed DSA on 90-d mortality among adult LDLT. These growing bodies

of evidence highlight the potential importance of the presence of preformed DSA in LT.

Currently, published articles on the utilization of antihumoral therapies for desensitization in DSA-positive liver transplant recipients are quite limited. Antihumoral agents and techniques used in kidney transplantation (plasmapheresis, intravenous immunoglobulin, rituximab, bortezomib, and eculizumab) are most commonly used as multimodality regimens, as shown in the present study, making the relative contribution of the component therapies difficult to ascertain.[6,18] In Asia, where rituximab induction is an established treatment for ABO-incompatible LDLT, some centers have reported the efficacy of rituximab desensitization for patients that are strongly sensitized for HLA.[26,27] In addition, adjunct treatments to rituximab will be matter of debate. Indeed, rituximab monotherapy was done for 12 patients (26%), and majority of cases were desensitized with additional treatments. Plasma exchange, which was performed in 57% in the present study, is a standard procedure to reduce DSA titers, but the titer required to prevent AMR is not defined. Some authors proposed DSA MFI 5000 as a guide.[20,26] IVIG is another standard procedure, especially for HLA-related DSA in kidney transplantation, and the IVIG dose often ranged from 0.1 to 2 g/kg.[3,4] In LT, some authors reported that IVIG was effective if preformed DSAs remain or de novo DSAs are detected,[28,29] however, it was used only in 2 patients in this series. The need for other drugs (calcineurin inhibitor, mycophenolate mofetil, and steroid) used as conventional immunosuppression after LT as a desensitization protocol should be investigated in future studies. Splenectomy is now considered unnecessary for desensitization.[30,31] While it was performed in 16 cases (34%) in this study, the aim was to modulate portal flow or to facilitate future antiviral treatment using interferon in hepatitis C patients. We herein report a nationwide survey of liver transplant recipients with preformed DSA with special reference to rituximab desensitization, which, to the best of our knowledge, is the largest series of desensitization for DSA-positive liver transplant recipients. This was a 1-arm observational study, however, and accordingly, the clinical effects of rituximab desensitization for preformed DSA require further investigation comparing with the control without desensitization. Nonetheless, the higher dose of rituximab reduced the incidence of AMR, indicating the possible efficacy of rituximab in preventing AMR due to preformed DSA. More importantly, our results revealed that intravenous rituximab was well tolerated among patients awaiting LT.

The A2ALL study group in the United States reported a similar incidence of preformed DSA, but a more significant effect in DDLT than in LDLT recipients.[32] In Japan, LDLT is the mainstay for LT, and indeed, in the present study, 81% of the cohort (38/47) underwent LDLT. In the LDLT setting, donors are often husbands, sons, and daughters for female recipients, who are likely to be strongly sensitized to DSA during pregnancy.[33,34] Actually, 92% (33/36) of the LDLT adult patients were female; 91% (30/33) had a history of pregnancy and 90% (27/30) received donations from their husbands or children. In contrast, in the LDLT setting, clinicians have enough time to prepare for preformed DSA as it is usually an elective operation, which may be an advantage compared with DDLT. Differences between DDLT and LDLT in regard to DSA are a matter of debate to be validated with a larger patient cohort to clarify whether graft type, quality, and injury determine outcomes in patients with DSA.

The present study has several limitations. First, this was a retrospective, 1-arm study. Because data of DSA-positive cases without rituximab desensitization were not collected, no comparison was possible between those with and without rituximab desensitization. Hence, the efficacy of rituximab desensitization should be evaluated in future prospective clinical trials. Second, the indication for the rituximab induction varied, both in terms of different assays and different cutoff values. Further research is necessary to identify which recipients with preformed DSA are at increased risk of post-transplant rejection and could receive maximal benefit by induction and enhanced immunosuppression. Third, we only assessed A/B/DR/DQ DSA and did not investigate Cw, DP, or non-HLA antibodies. Finally, liver biopsies were not protocol-based, but mostly on-demand procedures, which might have led to missed cases of AMR, especially chronic cases.

In conclusion, we confirmed the safety of a rituximab-based desensitization protocol for DSA-positive recipients with an acceptable incidence of infectious complications and relatively better graft/patient survival.

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