Original Article

No diffuse intrahepatic biliary stricture after ABO-incompatible adult living donor liver transplantation using tailored rituximab-based desensitization protocol

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Background: Rituximab (RTx) desensitization protocol offered good outcome in ABO-incompatible (ABOi) living donor liver transplantation (LDLT). However, diffuse intrahepatic biliary stricture (DIHBS) is still inevitable hurdle. We selectively added postoperative high dose intravenous immunoglobulin (IVIG) and/or simultaneous splenectomy if ABO isoagglutinin titer just before liver transplantation after plasma exchange (PE) was higher than 1/16. Herein, we reported the excellent outcome of ABOi LDLT without DIHBS using tailored desensitization protocol and compared it with that of ABO-compatible (ABOc) LDLT.

Methods: Sixty-five cases (14.8%) of ABOi LDLTs were performed among 438 primary adult LDLTs in our center between March 2012 and June 2017. We performed 1-to-2 propensity score matching (PSM) to extract 60 cases of ABOi LDLTs and 120 cases of ABOc LDLTs.

Results: There were no significant differences in clinical characteristics between ABOi and ABOc recipients. There were no significant differences in complications and rejection. There was no DIHBS in both groups. The 1-, 3-, and 5-year overall survival rates were 98.3%, 86.7%, and 82.9% in ABOi group and 96.7%, 86.7%, and 85.4% in ABOc group, respectively (P=0.88). Most common cause of deaths of both groups was hepatocellular recurrence. The 1-, 3-, and 5-year biliary complication (anastomosis leakage or stricture) free survival rates were 81.4%, 69.5%, and 67.5% in ABOi group and 83.0%, 81.3%, and 80.0% in ABOc group, with no significant differences (P=0.11).

Conclusions: RTx-based tailored (optional IVIG + splenectomy) desensitization protocol for ABOi LDLT was feasible and acceptable.

Keywords: Rituximab (RTx); ABO incompatible; liver transplantation (LT); desensitization

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Introduction

Rituximab (RTx) desensitization protocol in ABO-incompatible (ABOi) living donor liver transplantation (LDLT) offered a new paradigm shift beyond ABO blood barrier to obtain donor pool expanding (1). During the recent decade, high volume liver transplant centers mainly in east Asia have reported the feasibility and good outcome of RTx-based therapy without local infusion (2,3). However, diffuse intrahepatic biliary stricture (DIHBS) has been remained as an inevitable hurdle and reported 6.3–8% in recent reports (3-5) using RTx-based therapy. Therefore, various modifications in terms of plasmapheresis, splenectomy and intravenous immunoglobulin (IVIG) considering cost-effectiveness were proposed to overcome this hurdle. Here, in this study, we report the excellent outcome of ABOi adult LDLT without DIHBS using tailored desensitization protocol and compare it with that of ABO-compatible (ABOc) LDLT.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4703).

Methods

Study population and propensity score matching (PSM) (Figure 1)

Between March 2012 and June 2017, we performed 65 cases (14.8%) of ABOi LDLTs in our center among 438 primary adult LDLTs. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board (IRB) at Seoul National University Hospital (SNUH) number "1910-036-1068". Informed consent was waived by the IRB due to the retrospective study design. All methods employed in this study were performed in accordance with the relevant guidelines and regulations. One case was excluded due to insufficient data. We performed 1-to-2 PSM to extract ABOc cases. The propensity scores were generated using perioperative characteristics including age, sex, the etiology, the model for end-stage liver disease (MELD) score, the presence of hepatocellular carcinoma (HCC) or not, the level of alpha-fetoprotein (AFP) and PIVKA-II, final graft-to-recipient weight ratio (GRWR), cold ischemic time (CIT), recipient operative time, and recipient operative blood loss. Four cases of ABOi were excluded because of the mismatching of the propensity score. Finally, 60 ABOi cases and 120 ABOc cases were selected. The postoperative complication rates and overall survival (OS) and graft survival (GS) rates were then retrospectively compared between ABOc and ABOi cases.

Tailored desensitization and immunosuppression protocol for ABOi LDLTs

Our tailored desensitization protocol is shown in *Figure 2*.

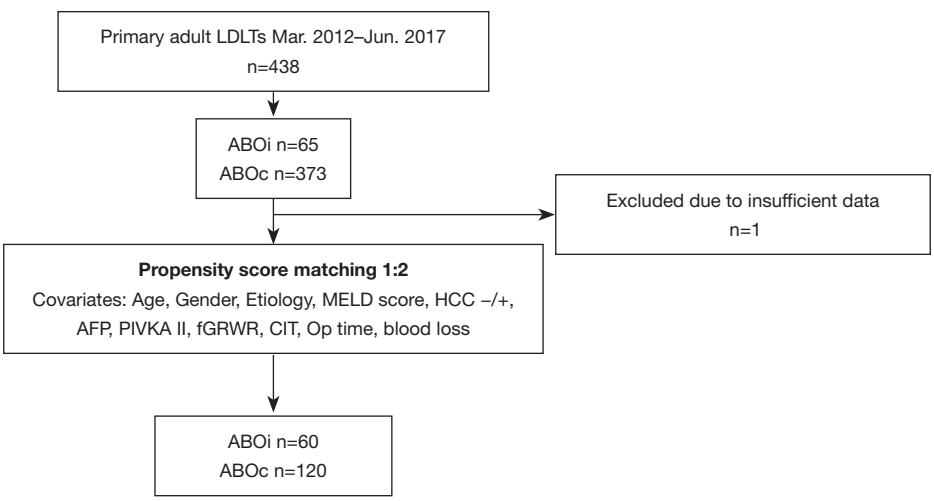

Figure 1 Study population and PSM analysis. We performed 1-to-2 PSM. Finally, 60 ABOi cases and 120 ABOc cases were selected. LDLT, living donor liver transplantation; ABOi, ABO-incompatible; ABOc, ABO-compatible; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; CIT, cold ischemic time; PSM, propensity score matching.

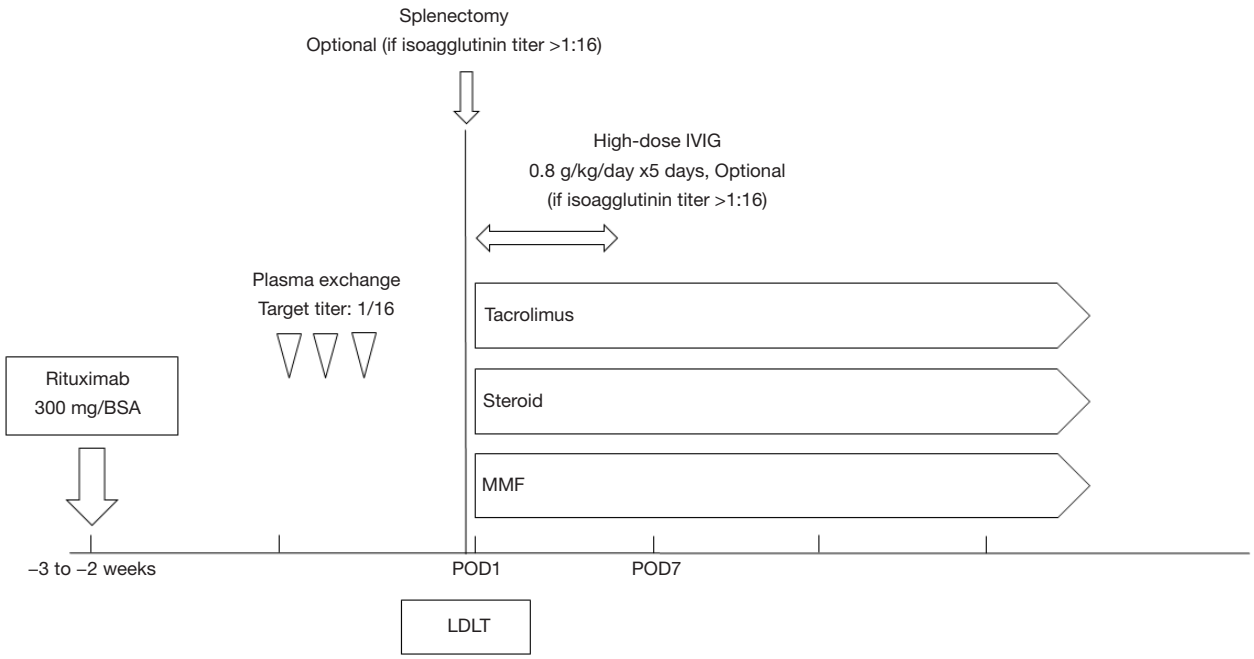

Figure 2 Immunosuppression protocol for ABOi LDLTs. Reduced RTx (300 mg/BSA) around 3 weeks before LDLT, followed by at least 3 times of plasma exchange (PE) at 1 week before LDLT regardless ABO isoagglutinin titer after RTx administration. Postoperative high dose intravenous immunoglobulin (IVIG, 0.8 g/kg) and/or simultaneous splenectomy were selectively added if ABO isoagglutinin titer just before liver transplantation (LT) was higher than 1/16. The immunosuppression was maintained with triple therapy (tacrolimus, steroids, and mycophenolate mofetil). LDLT, living donor liver transplantation; ABOi, ABO-incompatible; RTx, rituximab; BSA, body surface area; POD, postoperative day.

Reduced dose of RTx [300 mg/body surface area (BSA)] was administered around 3 weeks before LDLT, followed by 1 to 6 times of plasma exchange (PE) at 1 week before LDLT for a decrease of ABO isoagglutinin titer less than 1/16. If ABO isoagglutinin titer just before liver transplantation (LT) after PE was higher than 1/16, postoperative high-dose IVIG (0.8 g/kg/day of immunoglobulins were administered for 5 days from POD#1) and/or simultaneous splenectomy were selectively added. The splenectomy was sometimes skipped by surgeons' decision. In emergent cases, a limited number of PE was done 48 hours after RTx administration. Immunosuppression was maintained with triple therapy; tacrolimus, steroids, and mycophenolate mofetil (MMF). During operation, methylprednisolone, 500 mg, was given intravenously. Postoperatively, methylprednisolone was tapered from 200 to 40 mg/day over 5 days and discontinued within 3 months after the operation. MMF (1 g/day) was given orally from POD1. The administration of tacrolimus was delayed and started orally on POD2 or 3 while renal function returned. The therapeutic trough levels (5–10 ng/mL) of tacrolimus were achieved within 7 days after transplantation.

Follow-up protocol for ABOi LDLTs

All patients who underwent LT had daily blood tests for checking liver function and tacrolimus level. Doppler sonography was performed to evaluate postoperative anastomosis until 6 days postoperatively. Computed tomography and routine liver biopsy were performed on day 7 postoperatively. ABO antibody titer was measured 2, 5 and 7 days after surgery.

Cytomegalovirus (CMV) antigenemia was followed up twice a week until discharge and then once a month until 3 months after LT. IV ganciclovir (GCV) was given preemptively if CMV antigenemia test shows equal or more than 5 positive cells/2×10^5 polymorphonuclear leukocytes.

All patients were discharged 2 weeks after surgery without any special complications and visited every week during the month of discharge.

Table 1 Desensitization results for ABOi LDLT

Variables	ABOi (n=64)
The timing of RTx, days before LT, median [SD, range]	19 [6, 4–33]
Frequency of PE before LT, median [range]	3 [1–16]
ABO isoagglutinin titer, median [range]	
IgM initial	64 [2–512]
Pre-LT	2 [<1 to 64]
IgG initial	96 [2–1,024]
Pre-LT	16 [<1 to 512]
Pre-LT CD19, %, median [SD, range]	0.21 [3.4, N.D.–24]
Optional treatment, n (%)	
Splenectomy (%) + high-dose IVIG	12 (18.8)
High dose IVIG (%) only	8 (12.5)

Among 65 cases of ABOi cases, one case was excluded due to insufficient data. ABOi, ABO-incompatible; IVIG, intravenous immunoglobulin; LT, liver transplantation; PE, plasma exchange; RTx, rituximab; SD, standard deviation; N.D., not detected.

Magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiography (ERC) were considered if patients were suspected of biliary complications with liver function abnormality such as elevation of alkaline phosphatase or gamma-glutamyl transpeptidase, instead of a routine examination. DIHBS was defined as bilateral multifocal stricture or diffuse necrosis of intrahepatic bile ducts in cholangiographic appearance according to our previous study (6).

Statistical analyses

The continuous values were compared by using the Mann-Whitney U-test, and categorical data were compared by using the chi-square test or Fisher's exact test. The survival rates were estimated by the Kaplan-Meier method and compared in each group by the log-rank test. The significance threshold was $P<0.05$. PSM analysis was performed with SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA). Other statistical analyses were performed with GraphPad Prism version 7.03 (GraphPad, San Diego, CA, USA).

Results

Desensitization results in ABOi LDLT

The results of our desensitization for ABOi were shown in *Table 1*. The timing of RTx administration was 19 days before LT (range, 4–33 days). Median frequency of pre-transplant PE was 3 times (range, 1–16). However, two cases with initially high titer (1:1,024) received 14 and 16 times of PE for 2 to 3 weeks among the initial series. The median IgM and IgG titers before LT were 2 (range, <1 to 64) and 16 (range, <1 to 512), respectively. There were 8 cases (12.5%) with longer days more than 3 weeks after rituximab among 64 ABOi cases due to various reasons (multiple PE during more than 1 week, delayed due to donors' reasons, and so on). On the contrary, there were 3 emergent cases that the duration between RTx to LT was less than 1 week. Twelve recipients of ABOi series (18.8%) received simultaneous splenectomy and high-dose IVIG. Eight patients received perioperative high dose IVIG administration only.

The changes in isoagglutinin titer (IgG) was shown in *Figure 3* according to the desensitization methods. There are 9 cases (20.5%) of rebound in no additional treatment group, 3 cases (37.5%) in IVIG only group, and 0 cases in IVIG + splenectomy group. However, there was no difference in biliary complication rate between desensitization method.

Basiliximab was added to the triple therapy for only the initial case in our ABOi series.

Patient characteristics

The clinical characteristics between ABOi (n=60) and

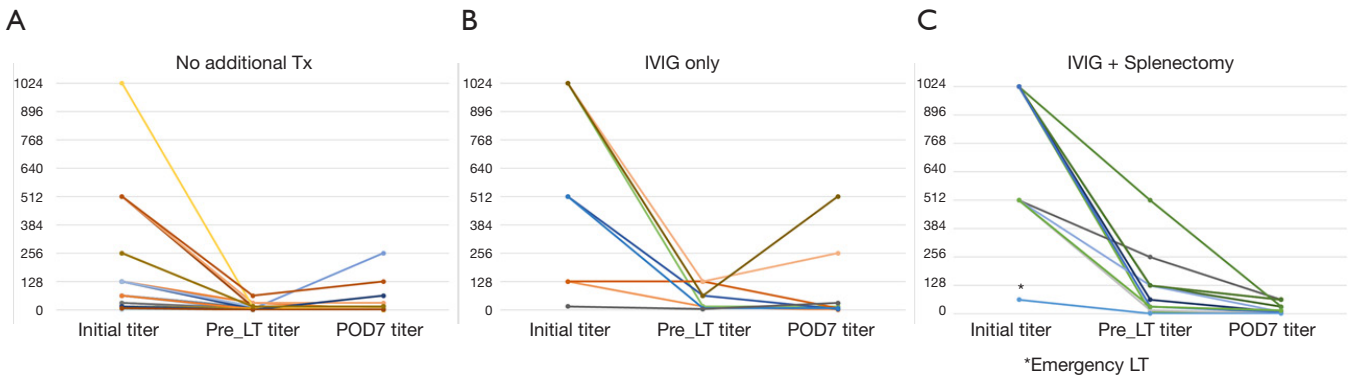

Figure 3 The changes in isoagglutinin antibody (IgG) titer according to the desensitization protocol. (A) No additional treatment group (n=44); (B) additional IVIG only group (n=8); (C) additional IVIG and splenectomy group (n=12). There are 9 cases (20.5%) of rebound in no additional treatment group, 3 cases (37.5%) in IVIG only group, and 0 cases in IVIG + splenectomy group. IVIG, intravenous immunoglobulin; LT, liver transplantation; POD, postoperative day.

ABOc (n=120) recipients after PSM are summarized in *Table 2*. There were no significant differences in clinical characteristics except for warm ischemic time (WIT) between ABOi and ABOc recipients. All recipients and donors were CMV IgG positive before LT.

Postoperative complications and cause of deaths

The minimum follow-up was more than 3 years in all cases. The median length of follow–up for censored cases was 57.6 months (range, 1–100.5 months) in ABOi cases and 61.2 months (range, 1–99.8 months) in ABOc cases, without significant difference. Postoperative complications are shown in *Table 3*. There were no significant differences in vascular, biliary, and infectious complications and rejection. Biliary complication tended to be a little higher in ABOi cases. However, we have not encountered DIHBS related to ABO-incompatibility. Acute cellular rejection which was proven by biopsy occurred 7 cases (11.7%) in ABOi group and 5 cases (4.2%) in ABOc group, but that was not statistically significant. We also had no experience of antibody-mediated rejection (AMR) proven by protocol biopsy at postoperative day (POD) 7 in both groups. Twelve recipients of ABOi cases (20.0%) had CMV infection, which was significantly higher than ABOc cases. There was no CMV disease with symptoms in ABOi cases.

OS, GS, and biliary complication free survival

The OS and GS were shown in *Figure 4*. There were no significant differences in 1-, 3-, and 5-year survival rates of ABOi and ABOc groups (*Figure 4A*). Two patients in the ABOi group received re-transplantation for graft failure due to hepatic artery thrombosis (HAT), and intractable hyperbilirubinemia on POD 22 and 764, respectively (*Figure 4B*). The latter patient showed mild dilatation of intrahepatic duct and small gas-containing biloma outside of the liver (around cut surface of the graft) on CT scan at 8 months after LT. Percutaneous trans-hepatic biliary drainage (PTBD) showed the anastomosis stricture, leakage, and common bile duct stones, however, all intrahepatic duct was normal appearance. Multiple PTBD procedures and frequent infection associated with the infected biloma containing the detached artificial graft in the graft for draining of the middle hepatic vein (MHV) tributaries resulted in liver failure. This patient received deceased donor LT at POD764. The pathologic findings of the explant liver were compatible with biliary cirrhosis.

Finally, both recipients could be rescued. There were 10 deaths (16.7%) in ABOi group and 19 deaths (15.8%) in ABOc group. Most common cause of deaths was HCC recurrence (70.0% in ABOi, 47.4% in ABOc group) (*Table 3*).

Biliary complication (anastomosis leakage or stricture) free survival was compared (*Figure 4C*). The 1-, 3-, and 5-year biliary complication free survival rates were 81.4%, 69.5%, and 67.5% in ABOi group and 83.0%, 81.3%, and 80.0% in ABOc group, with no significant differences (P=0.11).

Discussion

ABO blood type barrier was used to be a big obstacle for

Table 2 Comparison of clinical characteristics between ABOi and ABOc recipients after propensity score matching

Variables	ABOi (n=60)	ABOc (n=120)	P value
Recipient factors			
Age, years, median [SD, range]	54 [10, 27–77]	56 [8, 32–74]	0.55
Male gender, n (%)	42 (70.0)	83 (69.2)	>0.99
BMI, median [SD, range]	22.6 (3.6, 15.8–32.2)	22.2 (3.7, 15.5–34.0)	0.48
Etiology, n (%)			0.81
HBV (%)	41 (68.3)	84 (70.0)	
HCV (%)	7 (11.7)	10 (8.3)	
ALD (%)	6 (10.0)	16 (13.3)	
Others (%)	6 (10.0)	10 (8.3)	
MELD score, median [SD, range]	11 [8, 6–40]	13 [6.8, 6–34]	0.62
CP score, median [SD, range]	7 [2, 5–13]	6 [2.5, 5–13]	0.19
HCC+, n (%)	42 (70.0)	89 (74.2)	0.60
Graft factors			
Donor age, years, median [SD, range]	35 [12, 17–58]	33 [12, 16–60]	0.68
Donor male gender, n (%)	40 (66.7)	74 (61.7)	0.62
Final GRWR, median [SD, range]	1.16 [0.30, 0.56–1.94]	1.15 [0.29, 0.65–1.95]	0.56
CIT, min, median [SD, range]	72 [29, 31–174]	74 [24, 35–188]	0.62
WIT, min, median [SD, range]	25 [9, 11–59]	28 [10, 5–57]	<0.01
Operation factors, median [SD, range]			
OP time, min	335 [77, 260–550]	343 [80, 217–535]	0.25
Blood loss, g	1,450 [2,238, 200–12,100]	1,225 [3,249, 150–10,100]	0.60

ABOc, ABO-compatible; ABOi, ABO-incompatible; ALD, alcoholic disease; BMI, body mass index; CIT, cold ischemic time; CP, Child-Pugh; GRWR, graft-to-recipient weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease; OP, operative; WIT, warm ischemic time.

LT. Local infusion therapy made a big footstep to better outcome (7,8), however, the survival rate was not satisfactory compared to ABOc LT (9). Second impact, RTx, anti-CD20 human chimeric monoclonal antibody, offered paradigm shift to breakthrough into even comparable survival (1,2,5,10-12). RTx is a potent immune-modulational drug to deplete B cell which produces an antibody leading to deleterious humoral rejection. According to Japanese multicenter study, after induction of RTx desensitization therapy, the incidence of acute type AMR such as hepatic necrosis decreased from 23.5% to 6.3% (3). Desensitization therapy by RTx obtains a consensus among many transplant centers and has completely replaced as fist place instead of local infusion therapy (1,5,11,13,14).

However, mild form of AMR-related complications is not rare even with RTx with/without PE protocol. Song *et al.* reported in their large single center experience that 7.1% of patients experienced AMR-related complications, all in the form of DIHBS (5). According to recent reports from Korean centers, its incidence was 6.4–7.2% (4,5). DIHBS is still a desperate complication that is refractory to interventions and often required re-transplantation. Therefore, an additional strategy is necessary to reduce the risk of AMR, especially in high-risk patients. However, the risk factor of DIHBS has not been identified yet. Even though Song *et al.* did not find any correlation between pre-LT or post-LT isoagglutinin titers and the occurrence of DIHBS (5), there are several reports to show the

Table 3 Comparison of postoperative complications and cause of deaths during follow-up between ABOi and ABOc recipients

Variables	ABOi (n=60)	ABOc (n=120)	P value
Bleeding control* (%)	7 (11.7)	9 (7.5)	0.41
Biliary complication (%)	18 (30.0)	21 (17.5)	0.08
DIHBS (%)	0 (0.0)	0 (0.0)	>0.99
Vascular complication (%)	4 (6.7)	6 (5.0)	0.73
Artery (%)	3 (5.0)	1 (0.8)	0.11
Portal vein (%)	2 (3.3)	2 (1.7)	0.60
Hepatic vein (%)	1 (1.7)	4 (3.3)	0.67
Infectious complication (%)	18 (30.0)	23 (19.2)	0.13
Septic status (%)	8 (13.3)	9 (7.5)	0.28
Bacterial pneumonia (%)	3 (5.0)	13 (10.8)	0.27
Superficial SSI (%)	0 (0.0)	1 (0.8)	>0.99
Deep SSI (%)	4 (6.7)	3 (2.5)	0.22
CMV infection** (%)	12 (20.0)	7 (5.8)	<0.01
CMV disease*** (%)	0 (0.0)	1(0.8)	>0.99
Fungal infection (%)	1 (1.7)	2 (1.7)	>0.99
Rejection			
ACR (%)	7 (11.7)	5 (4.2)	0.11
AMR (%)	0 (0.0)	0 (0.0)	>0.99
Cause of deaths			–
Total number of deaths	10	19	
HCC recurrence	7 (70.0)	9 (47.4)	
De novo malignancies	0	4 (21.1)	
Infection	2 (20.0)	3 (15.8)	
Others	1 (10.0)	3 (15.8)	
Cause of deaths			
Follow-up period, months, median (range)	57.6 (1–100.5)	61.2 (1–99.8)	0.34

*, operation or intervention; **, >5 antigen-positive cells/200,000 cells in antigenemia assay; ***, CMV infection with any symptoms. ABOc, ABO-compatible; ABOi, ABO-incompatible; ACR, acute cellular rejection; AMR, antibody-mediated rejection; CMV, cytomegalovirus; DIHBS, diffuse intrahepatic biliary stricture; SSI, surgical site infection; HCC, hepatocellular carcinoma.

relationship of treatment non-responsive high isoagglutinin titers and AMR (3,15). We consider the patients with high titer even after RTx and PE therapy as a high-risk group. We applied additional strategy including IVIG and splenectomy in this high-risk group.

Even though a Japanese multicenter study concluded no significant additional effect of IVIG and raised the problem of cost (3). Several reports suggest IVIG was effective as a rescue of AMR and minimize the risk of AMR after ABOi LDLT (16-19). Therefore, considering potential effectiveness and cost-effectiveness, selective use of IVIG can be considered in the high-risk group. We compromised the use of IVIG and reached to optional use. So far, we never have AMR and DIHBS and this protocol is successful.

Splenectomy in ABOi LDLT is still a controversial issue. Kyoto group proposed that splenectomy does not

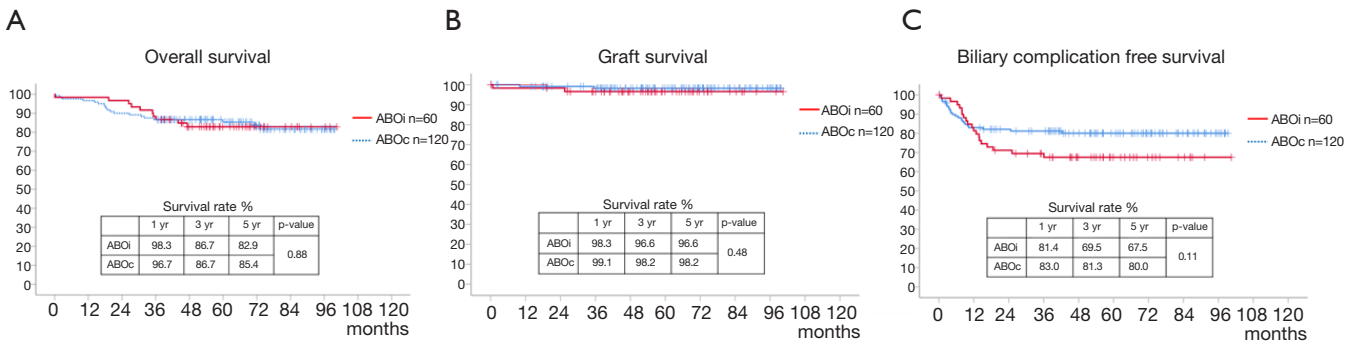

Figure 4 Comparison of the overall survival (A), graft survival (B), and biliary complication* free survival (C). There are no significant differences between two groups. *, biliary leakage or biliary stenosis. ABOi, ABO-incompatible; ABOc, ABO-compatible.

Table 4 Comparison of the desensitization protocol and outcomes (literature review)

Study	Number of ABOi cases enrolled	Details of desensitization methods				AMR associated DIHBS
		Rituximab	Plasmapheresis	IVIG	Splenectomy	
Kim *et al.* (2016) (4)	47	Yes	Yes	No	No	6.3%
Song *et al.* (2016) (5)	165	Yes	Yes	No	No	7.1%
Kim *et al.* (2018) (22)	43	Yes	No	Yes	No	0%
Kim *et al.* (2016) (19)	25	Yes	Yes	Yes	No	0%
Ikegami *et al.* (2016) (14)	19	Yes	Yes	Yes	Yes	0%
This study	64	Yes	Yes	Yes (optional, >1:16)	Yes (optional, >1:16)	0%

ABOi, ABO-incompatible; IVIG, intravenous immunoglobulin; AMR, antibody-mediated rejection; DIHBS, diffuse intrahepatic biliary stricture.

offer additional immunological benefits with preoperative RTx (20). A recent report showed a trend that splenectomy is omitted with RTx B cell depletion except for the case of acute liver failure in that each center has different strategies (15,21). However, a splenectomy can prevent maturation of reappeared B cell after LT, theoretically. Therefore, it can be also considered selectively if there is no increased risk of infection or surgical complications. We never experienced splenectomy-associated major operative complications nor fatal infection. We balanced the risk and effect of RTx and applied selective splenectomy depending on the response of isoagglutinin titer to pre-LT PE as best. Our protocol enabled us to adjust desensitization therapy such as combined splenectomy, and IVIG according to the risk of AMR. That's why we call our protocol "tailored". The different outcomes in terms of AMR associated DIHBS of the previous studies from the literature review and this study were shown in *Table 4*.

Interestingly, there was higher proportion of rebound in IVIG only group and no additional treatment group than that in IVIG + splenectomy even though the pre-LT isoagglutinin titer was higher than the other groups. However, there was no difference in terms of the rate of biliary complications between groups.

We started ABOi LDLT program from March 2012. We have performed 132 cases until the end of 2019. The proportion of ABOi LDLT has been increasing from 3.6% in 2012 to 30.0% in 2019. Different from other series, so far, we have not encountered clinically significant AMR related complications by this tailored RTx based desensitization protocol. Thus, this satisfactory outcome may encourage the feasibility of our current protocol and support to use ABOi donor to expand the donor pool for LDLT candidates. However, additional randomized controlled study or PSM study between this tailored protocol and RTx-based protocol without IVIG nor splenectomy among ABOi patients are needed to confirm the usefulness of this tailored protocol.

Japanese multicenter study reported that more than 300 mg/BSA of RTx induction was the risk factor of CMV disease in univariate analysis (3). In our series, CMV infection was significantly higher in ABOi group than in ABOc group. However, there was no CMV disease with symptoms in ABOi group. Finally, CMV infection could be controlled by valganciclovir (VGCV) or GCV therapy in all ABOi cases. Therefore, our protocol was considered acceptable in terms of prevention for an infectious complication.

Although further investigation is needed such as a nationwide study to identify the risk factor and best protocol, our protocol showed satisfactory results.

To date, many transplant centers deploy RTx desensitization protocol, but each group has own modification based on their experiences. Usually, 375 mg/BSA is the normal dose in ABOi LT. We used a slightly reduced dosage of RTx as 300 mg/BSA for potential risk of infection, resulting in no severe infection after ABOi LDLT. Toki *et al.* investigated that low dose RTx (<375 mg/BSA) on splenic B cell population in recipients of ABOi kidney transplantation and almost complete depletion of $CD20^+$ B cell from spleen (23). However, it is known that even in a single dose of 375 mg/BSA RTx could deplete almost all of B cell in the spleen and peripheral blood, the effect to lymph nodes is weak and memory B cell and plasma cell can survive in lymph nodes, at least 75% or more of whole peripheral lymphoid tissue (16,24,25). Egawa *et al.* reported that there was a tendency toward a higher incidence of AMR in patients treated with <300 mg/body compared with 500 or 375 mg/BSA (26). Therefore, we consider a reduced dose (300 mg/BSA) of RTx is a lower limit for balancing the prevention of AMR and severe infection.

About 70% of patients had HCC in our series. Because of B-cell depletion of RTx, there are concerns that the desensitization protocol might have a negative effect on HCC recurrence (27-29). However, our study focused on AMR related complications and infectious safety issues. Therefore, further study is needed to elucidate the oncological safety of our tailored protocol.

In conclusion, we haven't experienced clinically significant AMR including DIHBS related to ABO-incompatibility in our series. There were no significant differences in infectious complications between ABOc and ABOi cases. Therefore, our RTx-based tailored desensitization protocol for ABOi LDLT was feasible and the outcome was acceptable in terms of OS and AMR associated complications.

However, additional randomized controlled study or PSM study between this tailored protocol and RTx-based protocol without IVIG nor splenectomy among ABOi patients are needed to confirm the usefulness of this tailored protocol.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4703). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board (IRB) at Seoul National University Hospital (SNUH) number "1910-036-1068". Informed consent was waived by the IRB due to the retrospective study design. All methods employed in this study were performed in accordance with the relevant guidelines and regulations.

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