Insufficient pretransplant induction therapy is associated with diffuse intrahepatic cholangiopathy in ABO-incompatible living donor liver transplantation for acute liver failure

Chih-Yao Hu[a,b], Cheng-Yen Chen[a,b], Hsin-Lin Tsai[a,b,c], Hao-Jan Lei[a,b,d], Yi-Fan Tsou[a,b], Fang-Cheng Kuo[a,b], Pei-Chin Tsai[a,b], Meng-Hsuan Chung[a,b], Shu-Cheng Chou[c,b], Shen-Chih Wang[b,e], Cheng-Yuan Hsia[a,b,d], Che-Chuan Loong[a,b], Chin-Su Liu[a,b,c], Niang-Cheng Lin[a,b,*]

[a]Division of Transplantation Surgery, Department of Surgery, Taipei Veterans General Hospital, Taiwan, ROC; [b]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Division of Pediatric Surgery, Department of Surgery, Taipei Veterans General Hospital, Taiwan, ROC; [d]Division of General Surgery, Department of Surgery, Taipei Veterans General Hospital, Taiwan, ROC; [e]Department of Anesthesiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

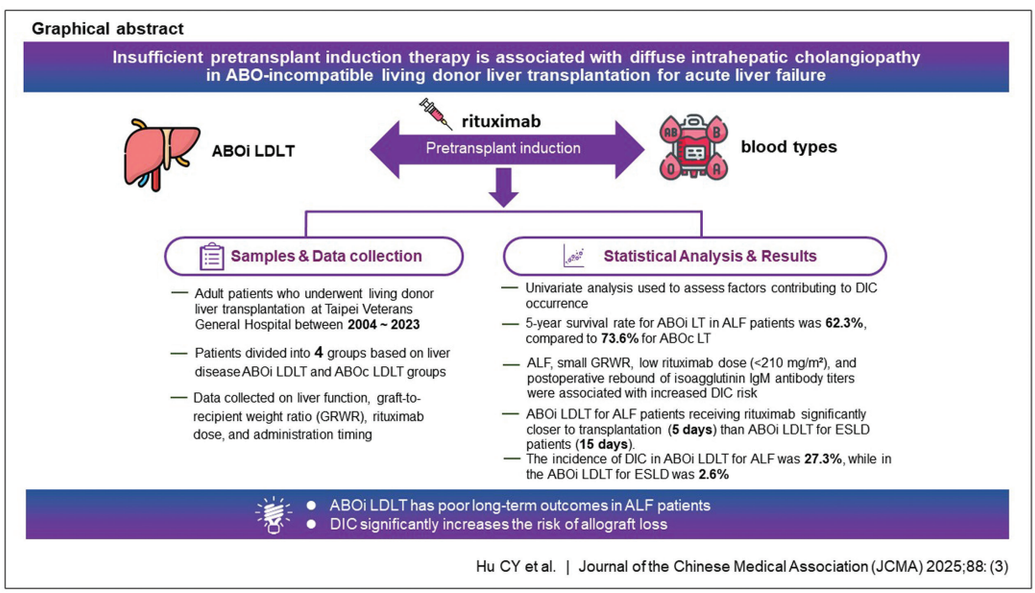
Background: ABO-incompatible liver transplantation (ABOi LT) can now be successfully performed using standard pretransplant induction therapy. ABOi LT can achieve long-term outcomes comparable to those of blood type-compatible (ABOc) LT. The outcomes of patients with acute liver failure (ALF) undergoing urgent transplantation surgery with a limited induction period require further investigation.

Methods: Between 2004 and 2023, adult patients who underwent living donor liver transplantation (LDLT) at Taipei Veterans General Hospital were included in this study. Patients were categorized into four groups for outcome analysis based on the chronicity of liver disease and transplant type. ALF patients who received ABOi LDLT, ALF patients who received ABOc LDLT, ESLD patients who received ABOi LDLT, and ESLD patients who received ABOc LDLT.

Results: Diffuse intrahepatic cholangiopathy (DIC) was observed in four cases within the ABOi LDLT group (n = 3, 27.3% in group 1; n = 1, 2.6% in group 3; $p = 0.03$). In ABOi LDLT patients, rituximab was administered closer to LT in group 1 (5 [3-6] days before LDLT) than that in group 3 (15 [14-22] days before LDLT) ($p < 0.01$). Univariate analysis identified ALF, a small graft-to-recipient weight ratio (GRWR), a low rituximab dose (<210 mg/m^2), and postoperative rebound of isoagglutinin immunoglobulin M (IgM) antibody titers as factors associated with an increased risk of DIC. Three out of four patients with DIC eventually experienced allograft loss. Overall, ABOi LDLT showed inferior long-term outcomes for ALF (5-year patient survival: 62.3%/73.6%/74.1%/76.7% in groups 1/2/3/4, respectively, $p = 0.25$).

Conclusion: ABOi LDLT achieved outcomes comparable to those of ABOc LDLT among ESLD patients but not among ALF patients. DIC is associated with a high risk of allograft loss. However, the combination of potent immunosuppressive agents, early detection of antibody rebound, and timely initiation of salvage treatment may improve long-term outcomes in these patients.

Keywords: ABO incompatibility; Diffuse intrahepatic cholangiopathy; Liver transplantation; Living donor



1. INTRODUCTION

Liver transplantation (LT) has become a crucial therapeutic option for individuals with end-stage liver disease (ESLD), a condition that presents significant health challenges. In Taiwan, the prominence of living donor liver transplantation (LDLT) has grown substantially, primarily due to the limited availability of deceased donor organs. The regulations governing LDLT in Taiwan are particularly stringent, limiting eligibility to individuals within a 5th-degree kinship and imposing specific physiological and psychological criteria for potential donors.[1] Although these stringent regulations are designed to ensure the careful evaluation and execution of the LDLT process, they also impose limitations on its availability. Consequently, ABO-incompatible (ABOi) LDLT from blood type-incompatible donors frequently becomes the only option.

ABOi LT using conventional immunosuppressants has historically been contraindicated due to the high risk of immune-related injury and allograft loss. In recent decades, the development of specific strategies focused on antibody depletion has improved transplant outcomes. In the early 2000s, Tanabe et al[2] introduced intraportal infusion therapy alongside plasmapheresis (PP) and splenectomy as antirejection strategies for ABOi LDLT. In addition, Nakamura et al[3] reported the use of intrahepatic artery infusion therapy. Local infusion therapy was a milestone in ABOi LDLT, significantly increasing 3-year patient survival from 29% to 56% while reducing the frequency of antibody-mediated rejection (ABMR) from 47% to 27%.[4] Following promising preliminary results, rituximab, a potent B-cell depletion agent, is now considered essential and has largely replaced intraoperative local infusion therapy and splenectomy. The cumulative 3-year patient survival rate has reached 92.3% in the rituximab era,[5] which is comparable to that of blood type-compatible (ABOc) LT.[6–8]

Acute liver failure (ALF) is a distinct and rapidly progressing disease. Without LT, the 3-month mortality rate exceeds 80%.[9] Taiwan is an endemic area of viral hepatitis with a high prevalence of chronic ESLD. It is estimated that more than 1000 candidates are registered on the waiting list for transplantation, while only approximately 100 liver grafts are available from deceased donors every year.[1] For patients with ALF, LDLT is usually the timelier option. With the success of patients with chronic ESLD, the use of ABOi LDLT has recently attracted increased attention for patients with ALF.[7,8,10] Although ABOi LDLT offers an alternative option, patients with ALF who are in urgent need of a transplant do not have a sufficient period of time for pretransplant induction therapy, which may impact post-transplant outcomes.[11]

This study aimed to compare LDLT outcomes between ABOi and ABOc patients, stratified by liver disease chronicity (ALF vs. ESLD), to evaluate disease-specific transplantation outcomes.

2. METHODS

2.1. Study cohort

Adult patients who received LDLT at Taipei Veterans General Hospital in Taiwan from October 2004 to August 2023 were enrolled. The medical records were retrospectively analyzed. Patients who died intraoperatively were not included. The enrolled patients were categorized into four groups based on the chronicity of their disease (ALF vs ESLD) and the type of LDLT (ABOi vs ABOc): group 1 (ALF patients who received ABOi), group 2 (ALF patients who received ABOc), group 3 (ESLD patients who received ABOi), and group 4 (ESLD patients who received ABOc).

2.2. Induction therapy protocol for ABOi LDLT

Patients undergoing ABOi LDLT follow a carefully structured preoperative regimen. This protocol consists of the use of an anti-CD20 monoclonal antibody (rituximab) for peripheral B-cell depletion 2 to 3 weeks before LT (with a fixed dose of 200 mg or 300-375 mg/m^2, based on the clinician's decision), followed by PP at 1 week before LT. The primary aim is to attain an isoagglutinin immunoglobulin G (IgG) antibody titer (anti-A antibody in the case of donor blood type A to recipient blood type B or O, and anti-B antibody in the case of donor blood type B to recipient blood type A or O) below the target threshold of 32. In cases of high immunological risk, intravenous immunoglobulin therapy (IVIG) is considered after PP, and an anti-CD25 monoclonal antibody (basiliximab) is given during the perioperative period (20 mg on days 0 and 4). For patients with ALF, the interval between rituximab administration and surgery was not restricted by the protocol. Sulfamethoxazole (400 mg) + trimethoprim (80 mg) and acyclovir (200 mg daily) are used as antiviral agents for prophylaxis of Pneumocystis jirovecii pneumonia (PJP).

2.2.1. Measurement of isoagglutinin antibody titers

Plasma (0.5 mL) is collected, and consecutive 2-fold dilutions of serum are prepared with saline. A pipette is used to transfer 0.1 mL of the diluted serum into a test tube, which is marked appropriately. Then, 0.05 mL of red blood cell suspension (2%-5%) is added, and the mixture is mixed well. The samples are immediately centrifuged, and the saline concentration is measured at room temperature. After a 30-minute incubation at 37°C, an anti-IgG test is performed to obtain the IgG titer. The highest dilution that produces 1+ macroscopic agglutination is determined. The titer is reported as the reciprocal of the dilution level. The measured isoagglutinin IgM/IgG antibody titer was specific to the donor blood type. A rebound in the isoagglutinin antibody titer is defined as an increase in the postoperative titer compared with that on the day before surgery.

2.3. Lymphocyte surface marker measurements

Peripheral blood lymphocyte antigens were analyzed to assess immune status through quantitative measurement of four subsets: CD3+ T cells, CD19+ B cells, CD3+/CD4+ helper T cells, and CD3+/CD8+ cytotoxic T cells. Fresh blood (2 mL) was collected in ethylenediaminetetraacetic acid (EDTA) tubes and processed within 6 hours to ensure cell viability. Flow cytometry was conducted using a DxFLEX automated 13-color

*Address correspondence: Dr. Niang-Cheng Lin, Division of Transplantation Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: nclin@vghtpe.gov.tw (N.-C. Lin).

Conflicts of interest: Dr. Chin-Su Liu, an editorial board member at the Journal of the Chinese Medical Association, had no role in the peer review process or decision to publish this article. The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2025) 88: 222-230.

Received August 1, 2024; accepted December 6, 2024.

doi: 10.1097/JCMA.0000000000001211

fluorescence cytometer and the monoclonal antibodies CYTOSTAT tetraCHROME® CD45-FITC/CD4-RD1/CD8-ECD/CD3-PC5 and CD19-PC7. CD19 expression is similar to that of CD20 but persists throughout the entire B-cell development process, whereas CD20 is lost upon plasma cell differentiation. Studies indicate CD19 is a reliable marker; therefore, we used CD19 to assess peripheral B-cell depletion in rituximab-treated patients.[12,13]

2.4. Surgical procedure

Intravenous methylprednisolone therapy (MPT) is administered intraoperatively at a dose of either 500 or 1000 mg just before graft anastomosis. To ensure optimal organ preservation, a histidine-tryptophan-ketoglutarate (HTK) solution is administered. Biliary anastomosis was primarily performed using duct-to-duct anastomosis with 6-0 absorbable sutures. For patients who could not undergo duct-to-duct anastomosis, Roux-en-Y anastomosis was performed.

2.5. Postoperative immunosuppression protocol

The post-transplant immunosuppressive regimen is based on tacrolimus. Tacrolimus is introduced orally starting on postoperative day (POD) 1. The dose is carefully titrated to maintain blood levels within the target range of 5 to 7 ng/mL. Intravenous MPT is administered at a dose of 125 mg every 6 hours on POD 1. The dosage is gradually reduced, transitioning to oral prednisolone on POD 5. If suitable, this treatment may be stopped after three months. Mycophenolate mofetil (MMF) is administered once the patient's platelet count exceeds 100,000. For patients who are positive for hepatitis B virus (HBV), the post-transplant regimen includes a 7-day course of Hepatect with life-long antiviral therapy for HBV. The prophylactic antibiotics administered included trimethoprim/sulfamethoxazole and acyclovir.

2.6. Definition of diffuse intrahepatic cholangiopathy and graft failure

The diagnosis of diffuse intrahepatic cholangiopathy (DIC) relies on biopsy reports and imaging findings. Imaging modalities that are used before biopsy include abdominal computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography (PTC). These imaging studies reveal characteristic patterns of diffuse intrahepatic biliary strictures, with the exclusion of hepatic artery thrombosis (HAT). Biopsy specimens are used to confirm the diagnosis. In cases where biopsy samples show evidence of biliary obstruction and ischemic features, DIC is considered. Graft failure is defined as the need for liver retransplantation or the presence of clinical signs consistent with ESLD.

2.7. Statistical analyses

Categorical variables were analyzed using Fisher's exact test, while continuous variables were assessed using the Mann–Whitney test. Data are presented as the median with first and third quartiles. Survival probability was evaluated through Kaplan–Meier analysis and compared using both the log-rank and Breslow tests. To assess the associations between various factors and the incidence of DIC, logistic regression analysis was used. Receiver operating characteristic (ROC) analysis and Youden index calculation were used to determine the optimal preoperative rituximab dose (mg/m²) cutoff for predicting DIC. All p values reported in this study were derived from two-sided tests, and p values less than 0.05 were considered to indicate statistical significance. Data analysis was conducted using SPSS version 26.0 (IBM, Armonk, NY).

3. RESULTS

3.1. Patient demographics

A total of 464 adult patients underwent LDLT at our center from October 2004 to August 2023. Among them, five patients were excluded from the outcome analysis, including one patient who had undergone LT in China and subsequently returned to our center, one patient who had undergone transplantation for noncirrhotic liver disease (familial amyloid polyneuropathy), one patient with incomplete post-LT follow-up, and two patients who underwent dual-graft LDLT. The remaining 459 patients were divided by donor–recipient blood type compatibility (ABOi, n = 50 vs ABOc, n = 409) and the chronicity of their liver disease (acute, n = 93 vs chronic, n = 366) into four groups: group 1 (ALF patients who received ABOi; n = 11), group 2 (ALF patients who received ABOc; n = 82), group 3 (ESLD patients who received ABOi; n = 39), and group 4 (ESLD patients who received ABOc; n = 327) (Fig. 1). Their demographic data are summarized in Table 1. The etiology of liver disease did not differ among the four groups; however, the MELD score was significantly greater among patients with ALF (groups 1 and 2), and the incidence of concurrent hepatocellular carcinoma was significantly greater among patients with ESLD (groups 3 and 4) ($p < 0.01$). The perioperative outcomes, including the cold ischemic time (CIT), warm ischemic time (WIT), total operation time, and blood loss, were not different among the four groups.

3.2. Overall patient and graft survival

The minimum follow-up period was 6 months. After a median follow-up of 57.5 months (interquartile range: 17.2–103.1), 34 cases of graft failure and 118 patient deaths were recorded. Graft survival was significantly lower among group 1 patients than among those in the other three groups ($p = 0.04$) (Fig. 2 and Supplement Table 1, http://links.lww.com/JCMA/A308). Patient survival was also significantly lower among group 1 patients in the short term ($p = 0.02$ according to the Breslow test), and while this difference was maintained over time, the statistical significance gradually decreased over the long term ($p = 0.09$ according to the log-rank test) (Fig. 2).

3.3. ABOi LDLT patients

All 50 patients received the B-cell depletion agent rituximab as a pretransplant induction agent, and the dose did not differ between the two groups (group 1: 269.4 [196.7-304.7] mg/m²; group 3: 281.06 [239.81-306.75] mg/m², $p = 0.44$). Only four patients in group 1 received pretransplant PP (4/11, 36.4%), which was lower than the number of patients who received PP in group 3 (25/39, 64.1%) ($p = 0.17$). The isoagglutinin titer, in terms of serum IgG, did not differ between the two groups at baseline and pre-LT, but the immunoglobulin M (IgM) antibody titer was significantly lower at baseline among group 1 patients ($p = 0.016$). Similarly, there were no significant differences in the baseline CD4 and CD19 levels between the two groups, but significantly lower CD4 counts (group 1: 184.6 [69.8-282.0]/CUMM, group 3: 324.0 [233.5-436.1]/CUMM, $p = 0.043$) and a greater percentage of CD19+ cells (group 1: 0.47% [0.23%-0.82%], group 3: 0.1% [0%-0.2%], $p < 0.01$) were noted among group 1 patients before the operation.

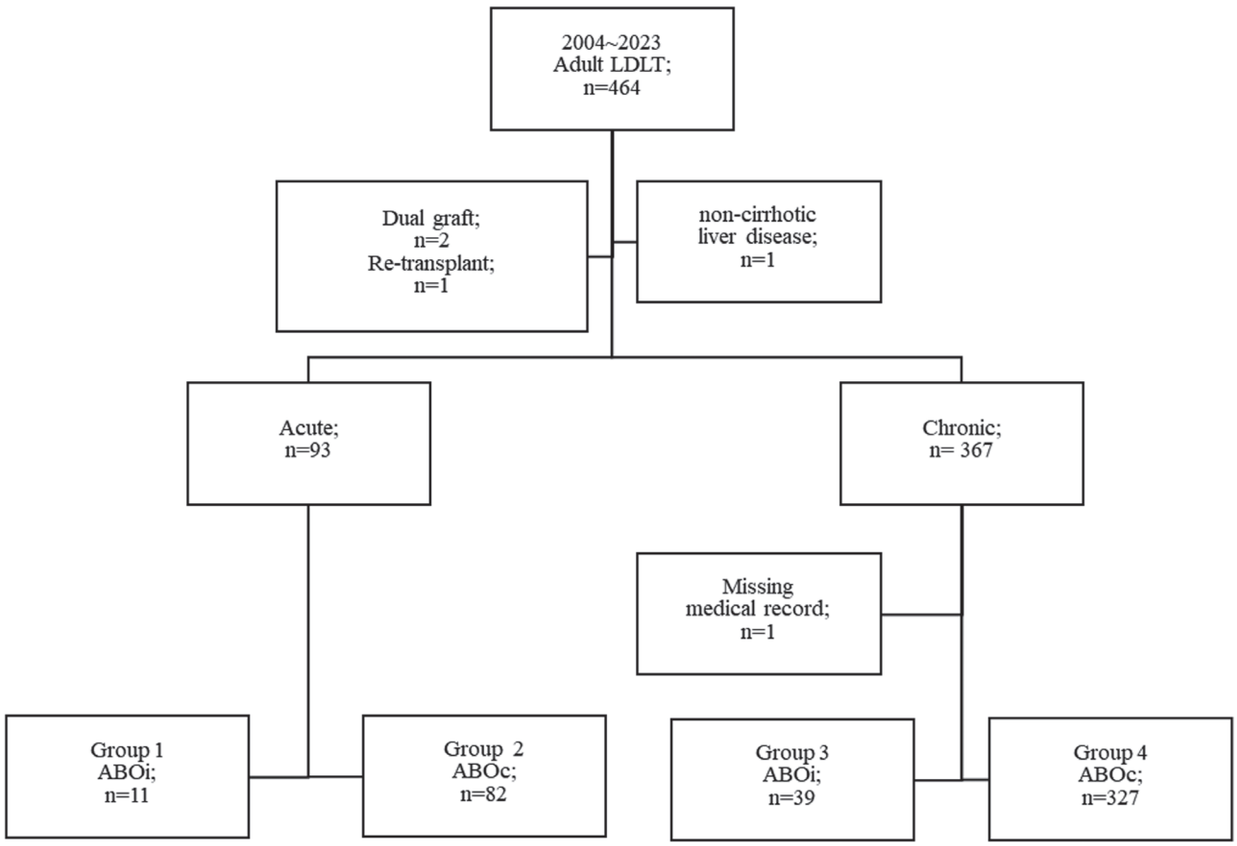


Fig. 1 Stratification of the study group. ABOc = ABO compatible; ABOi = ABO incompatible; LDLT = living donor liver transplant.

The incidence of isoagglutinin titer rebound and tacrolimus trough levels on POD 7 did not differ between the two groups. However, salvage PP was administered more frequently in group 1 than in group 3 (6/11 vs. 4/39, $p < 0.01$) (Table 2).

3.3.1. Diffuse intrahepatic cholangiopathy

No cases of DIC were reported among patients who underwent ABOc LDLT (groups 2 and 4). Among ABOi LDLT recipients, three patients in group 1 and one patient in group 3 were diagnosed with DIC. (as shown in Table 3 and Supplement Table 2, http://links.lww.com/JCMA/A308). Notably, the incidence of DIC and portal vein thrombosis (PVT) was higher in group 1 than in group 3 (3 vs. 1 patient, $p = 0.03$).

The clinical and histological findings of these patients are illustrated in Table 4, while Fig. 3 displays images of ERCP conducted both before and upon the diagnosis of DIC.

Univariate logistic regression analysis identified ALF, a small graft-to-recipient weight ratio (GRWR), a low rituximab dose (<210 mg/m^2), and postoperative rebound of isoagglutinin IgM antibody titers as risk factors for DIC. However, despite applying multivariate analysis techniques, including forward stepwise and backward step selection, no independent risk factor or best-fit model for DIC was identified. (Supplement Table 3, http://links.lww.com/JCMA/A308).

4. DISCUSSION

Both short- and long-term outcomes of ABOi LDLT were comparable to those of ABOc LDLT in patients with ESLD (groups 3 and 4). The 3-month cumulative patient survival rates were 100% in group 3 and 89.0% in group 4 ($p = 0.03$), while the 3-year cumulative patient survival rates were 83.4% in group 3 and 81.6% in group 4 ($p = 0.49$). These results align with the patient survival rates reported in the literature for ABOi LDLT, which range from 71% to 92.3%.[5,14–16] For ALF patients undergoing transplantation, increased disease severity and perioperative risks can lead to significantly different outcomes compared to those with ESLD. In our study, the 3-month patient survival rates after LDLT were notably lower among ALF patients than among ESLD patients (81.8% and 79.2% in groups 1 and 2, respectively, vs 100% and 89.0% in groups 3 and 4, respectively; $p = 0.01$). Furthermore, we observed a high incidence of DIC among patients in group 1 who underwent ABOi LDLT for ALF. DIC resulted in recurrent cholangitis and refractory jaundice, significantly affecting long-term graft outcomes (3-year graft survival rates of 60%, 92.6%, 95.2%, and 93.1% in groups 1, 2, 3, and 4, respectively; $p = 0.03$).

The overall incidence of DIC in our study was 8% (3 patients in group 1 and 1 patient in group 3), consistent with findings from a previous study on ABOi LDLT.[5] Song et al[5] reported a 7.2% incidence of DIC in patients who underwent ABOi LDLT with a desensitization protocol including the administration of rituximab (300-375 mg/m^2) 2 to 3 weeks before transplantation with PP tailored to isoagglutinin titers <1:8 before transplantation. Interestingly, neither the interval between rituximab administration (with a 2-week cutoff) nor the initial and post-LT peak isoagglutinin titers were identified as risk factors. However, none of the patients underwent emergency LT (the pre-LT hospital stay was 14.2 ± 13.1 [5–63] days), and only 1 (0.04%) patient presented with ALF.[5] In a study primarily involving ALF patients, Shen et al[7] demonstrated that ABOi LDLT could achieve patient

Table 1

Patient demographics

Demographic	Group 1	Group 2	Group 3	Group 4	*p*
Recipient age (y)	54 [47, 61]	55.5 [50, 62]	59 [54, 63]	57 [0, 62]	0.07
Donor age (y)	27 [23, 43]	31 [25, 39]	33 [26, 39]	31 [26, 41.3]	0.49
Male[a]	9 (81.8%)	62 (74.7%)	27 (69.2%)	227 (69.4%)	0.59
Gender[b]	7 (63.6%)	23 (27.7%)	14 (35.9%)	96 (29.4%)	0.08
Underlying disease					
HBV	7	69	13	117	
HCV	1	1	3	58	
ALD	1	4	6	49	
Cryptogenic	0	1	2	9	
PBC	0	1	1	6	
Autoimmune	0	0	0	7	
Wilson's disease	0	0	0	7	
HBV + HCV	0	1	2	7	
HBV + ALD	1	1	1	13	
HCV + ALD	0	0	2	2	
Only HCC	1	1	8	28	
Others	0	2	0	13	
Unknown	0	1	1	11	
HCC	2	7	26	154	<0.01*
GRWR (%)	1.1 [0.8, 1.2]	1.0 [0.9, 1.1]	1.0 [0.9, 1.2]	1.1 [0.9, 1.3]	<0.01*
MELD score	32 [25, 42]	36 [31.8, 40]	15 [11, 22]	17 [11.8, 27]	<0.01*
CIT (min)	60 [40, 92]	66 [43.8, 91.8]	63 [42, 112]	52 [40, 84.5]	0.86
WIT (min)	34 [29, 44]	38 [32, 47]	42 [33, 50]	39 [31, 51.3]	0.30
Operation time (min)	825 [755, 870]	777.5 [688.5, 851.8]	780 [715, 880]	782.5 [716.5, 861.3]	0.67
Blood loss (mL)	3865 [3100, 11475]	5025 [2777.5, 7000]	3410 [2360, 5370]	4259 [2796.3, 7150]	0.13
Patient follow-up time (mo)	9.3 [5.1, 69.2]	92.7 [26.7, 130.6]	36.3 [13.1, 61.6]	36.6 [16.2, 66]	0.02*

Others: HEV, angiosarcoma, cholangiosarcoma, epithelioid hemangioepithelioma, BT-IPMN, hepatitis, Budd-Chiari syndrome, polycystic liver disease, secondary biliary cirrhosis, ALD + angiosarcoma, HBV + HCV + chaolangiosarcoma, PBC + ALD, PBC + HCV.

ALD = alcoholic liver disease; BT-IPMN = biliary tract intraductal papillary mucinous neoplasm; CIT = cold ischemic time; GRWR = graft-to-recipient weight ratio; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HEV = hepatitis E virus; MELD = model for end-stage liver disease; PBC = primary biliary cirrhosis; WIT = warm ischemic time.

[a]Recipient gender.

[b]Female donor to male recipient.

*$p < 0.05$.

survival rates comparable to those of ABOc LDLT when using a specific induction protocol comprising an anti-CD20 monoclonal antibody, IVIG, and an anti-CD25 monoclonal antibody. However, despite this protocol, two cases of ABMR, including one case of intrahepatic bile duct complication and one case of hepatic necrosis, were still observed in the ABOi group (2/35, 5.7%). No cases of DIC were reported in the ABOc group in our study or in Shen's series.[7] Blood group antigens are known to be distributed in the intrahepatic ducts and ductules.[17,18] These findings suggest that DIC can be a disease-specific comorbidity in ABOi LDLT and warrants further investigation.

Although DIC could be a distinct disease pattern in ABOi LDLT, the incidence in our group of ALF patients (3/11, 27.3%, in group 1) was higher than what has been reported in the literature.[7,16,19] Furthermore, our analysis highlighted a small GRWR and postoperative rebound of isoagglutinin IgM titers as potential risk factors for DIC (Supplement Table 3, http://links.lww.com/JCMA/A308). In our study, we observed no significant difference in the dose of rituximab or IVIG for desensitization between group 1 (ALF) and group 3 (ESLD) patients. To mitigate the risk of life-threatening opportunistic infections in immunocompromised patients, we tended to administer lower doses of rituximab for both ALF and ESLD patients before ABOi LDLT (269.4 mg/m^2 in group 1 and 281.1 mg/m^2 in group 3, $p = 0.44$), which is considerably lower than the recommended dose cited in the literature.[2–11,16] In our study, the preoperative doses of rituximab used for the four patients with DIC were 188.6, 206.3, 329, and 200.6 mg/m^2. Three of the four patients received notably lower doses of rituximab than the recommended dose (375 mg/m^2) in the literature (Table 2). Analysis of the ROC curve for preoperative rituximab dose in predicting DIC revealed a cutoff of 209.6 mg/m^2, yielding the highest Youden index (sensitivity of 75% and specificity of 80.4%, with an area under the curve [AUC] of 0.67) (Supplement Fig. 1, http://links.lww.com/JCMA/A308). Furthermore, when we categorized our ABOi LDLT patients into two groups based on a preoperative rituximab dose threshold of 210 mg/m^2, doses below this threshold were identified as a risk factor for DIC in univariate logistic regression analysis (Supplement Table 3, http://links.lww.com/JCMA/A308). Therefore, the notably higher preoperative CD19 levels after desensitization in group 1 patients, coupled with clinical evidence of isoagglutinin rebound post-transplantation as a risk factor for DIC and histological findings on liver biopsies indicating humoral responses leading to allograft injury (eg, periportal inflammation, endotheliitis, positive C4d staining, microvasculitis, bile duct injuries with ductular reaction), suggest that reduced-dose rituximab therapy may be effective for patients with ESLD but not for patients with ALF requiring urgent transplantation with a limited peritransplant induction period. Therefore, a tailored pretransplant induction protocol should be developed.

In the context of ABOi LDLT for ALF,[20] Hsu et al[16] introduced a fast-track desensitization protocol, which involved rituximab (200 mg) administration 4 to 10 days before transplantation and four sessions of double-filtration PP (DFPP) in combination with basiliximab (20 mg intraoperatively and on POD

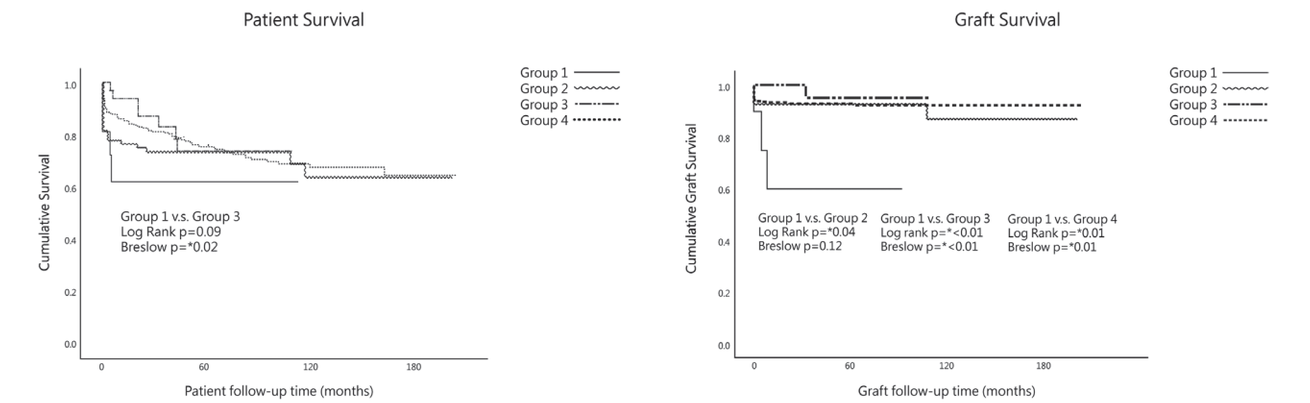


Fig. 2 Patient survival and graft survival of the four study groups.

Table 2

Management of isoagglutinin Ab in ABOi LDLT patients

Data and management	Group 1	Group 3	*p*
Isoagglutinin titer (IgM)			
Baseline	16 [8, 16]	32 [16, 32]	0.02*
Before OP	8 [2, 16]	16 [8, 32]	0.65
Isoagglutinin titer (IgG)			
Baseline	32 [16, 64]	64 [32, 128]	0.09
Before OP	4 [2, 8]	16 [16, 32]	0.29
CD 4			
Baseline	347 [190.6, 440.2] (n = 5)	325.5 [244.5, 459.3] (n = 16)	0.78
Before OP	184.6 [69.8, 282] (n = 8)	324 [233.5, 436.1] (n = 29)	0.04*
CD 19			
Baseline	20.6 [15.6, 39.4] (n = 5)	16 [9.5, 23.3] (n = 16)	0.31
Before OP	0.5 [0.2, 0.8] (n = 8)	0.1 [0, 0.2] (n = 30)	<0.01*
Preoperative desensitization			
Rituximab	11	39	
Rituximab induction time (days pre-OP)	5 [3, 6]	15 [14, 22]	<0.01*
IVIG	2	9	>0.99
PP	4	25	0.17
Basiliximab	0	2	>0.99
Desensitization dosing			
Rituximab(mg/m^2)	269.4 [196.7, 304.7]	281.1 [239.8, 306.8]	0.44
IVIG (g/kg)	159.5 and 121.6 (n = 2)	489.1 [196.1, 616.1] (n = 9)	0.07
Splenectomy	1	2	0.53
Post-OP IgM rebound	2	10	>0.99
Post-OP IgG rebound	2	3	0.30
Post-OP salvage			
Rituximab	0	2	1.00
IVIG	2	5	0.64
PP	6	4	<0.01*
MPT	3	4	0.17
Salvage dosing			
Rituximab (mg/m^2)	0	200 (n = 2)	
IVIG (g/kg)	86.5 and 148 (n = 2)	867.1 [294.1, 917.4] (n = 5)	0.10
POD 7 tacrolimus level (ng/mL)	7.4 [5.5, 10.5]	7 [6.1, 8.5]	0.60
POD MMF	7	27	0.73

Ab = antibody; ABOi LDLT = ABO incompatible living donor liver transplantation; IgG = immunoglobulin G; IgM = immunoglobulin M; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; MPT = methylprednisolone pulse therapy; OP = operative; POD = postoperative day; PP = plasmapheresis.

*p< 0.05.

4) as an induction agent. With this protocol, 8% of patients were diagnosed with DIC, three of whom exhibited evidence of ABMR.[16] In a series from China, basiliximab was administered alongside a more potent dose of rituximab (a single dose of 375 mg/m^2 on the transplant day) and IVIG (0.4 mg/kg/d for 10 days) to ALF patients undergoing preparation for ABOi LDLT. This approach notably reduced the incidence of DIC to 2.9% (1/35). However, one patient experienced ABMR

Table 3

Disease-specific comorbidities in ABOi LDLT patients

Comorbidity	Group 1	Group 3	*p*
Biopsy finding			
TCMR	2	3	0.30
ABMR	0	0	
Vascular			
HAT	1	1	0.40
PVT	3	1	0.03*
Biliary			
Anastomotic	1	12	0.25
DIC	3	1	0.03*
Infection			
CMV	0	2	>0.99
Bacteria	2	9	>0.99
Fungus	2	3	0.30

ABMR = antibody-mediated rejection; ABOi LDLT = ABO incompatible living donor liver transplantation; CMV = cytomegalovirus; DIC = diffuse intrahepatic cholangiopathy; HAT = hepatic artery stenosis; PVT = portal vein thrombosis; TCMR = T cell-mediated rejection.
*$p < 0.05$.

and hepatic necrosis but was successfully treated with a high dose of IVIG (0.8 g/kg/d) combined with plasma apheresis. Lee et al[19] proposed a quick preparation regimen for patients with ALF before ABOi LDLT, which included bortezomib (3.5 mg) and PP to achieve an isoagglutinin titer ≤1:64 before transplantation, followed by rituximab (375 mg/m^2) on POD 1. Among eight patients who received this regimen, one patient (12.5%) was diagnosed with DIC and subsequently passed away. Notably, another patient in this group died due to fatal infectious comorbidities (PJP).[19]

Based on evidence from the literature, we believe that the incidence of DIC among ALF patients who have received ABOi LDLT could be significantly reduced by using induction strategies that involve T-cell inactivation or plasma cell apoptosis, in addition to potent doses of B-cell depletion agents, to improve long-term outcomes.[21] Given the increased risk of lethal complications and poorer perioperative outcomes associated with ABOi LDLT among ALF patients, there may be a tendency within the transplant community to adopt a more conservative approach, with ABOi LDLT potentially considered a contraindication for ALF patients. However, given the exceedingly high mortality rates among ALF patients without LT (3-month mortality rate exceeding 80%[9]) and the persistent shortage of organs from deceased donors, we propose that ABOi LDLT could still be a viable option for ALF patients with adequate pretransplant induction using a combination of potent immunosuppressants. Close monitoring of post-transplant isoagglutinin titers is essential, and in cases where titers rebound after transplantation, high-dose IVIG can be explored as a salvage treatment option.[2] Natsuda et al[22] implemented a tailored protocol involving high-dose IVIG (0.8 g/kg/d for 5 days) combined with selective splenectomy for patients with ABO isoagglutinin titers exceeding 1:16. Remarkably, none of the 60 patients who underwent ABOi LDLT under this protocol developed DIC.[22] In cases where DIC is confirmed, early retransplantation should be considered to prevent life-threatening complications associated with recurrent cholangitis.

Several limitations exist in this study. First, its retrospective design introduces the possibility of selection bias. To enhance the cohort's homogeneity for robust analysis, certain patients, such as noncirrhotic patients (n = 1), dual-graft patients (n = 2), patients who did not undergo initial transplantation at our hospital (n = 1), and patients with missing data (n = 1), were excluded. Second, the study spanned a 19-year period, during which technological advancements may have influenced patient outcomes. Third, there might be variations in desensitization methods and techniques among transplant surgeons in our center. Nonetheless, it is notable that the preoperative doses of rituximab and IVIG and the perioperative outcomes (including the CIT, WIT, operation time, and blood loss) were consistent across the study groups. Last, the study was conducted at a single medical center, limiting the generalizability of the findings. Future research involving multiple centers could provide a more comprehensive understanding of the topic.

In conclusion, ABOi LDLT achieved outcomes comparable to those of ABOc LDLT among patients with ESLD but not ALF. In addition, patients who received ABOi LDLT for ALF were at increased risk of DIC, which can result in allograft failure after transplantation. The reduced dose of rituximab (<210 mg/m^2) and insufficient induction period may partly

Table 4

Clinical and histology findings of patients with diffuse intrahepatic cholangiopathy

Clinical and histology finding	Case 1	Case 2	Case 3	Case 4
Age at transplant	62	53	47	60
Rituximab mg(/BSA); days before LDLT	400 (188.6); 3 d	350 (206.3); 5 d	600 (329); 6 d	200 (200.6); 15 d
Onset of DIC (by image)	POD 30	POD 130	POD 12	POD 76
Biopsy time	POD 31	POD 130	POD 12	POD 119
Splenectomy	No	No	No	No
Bile duct anastomosis	Duct to duct	Duct to duct	Duct to duct	Duct to duct
Isoagglutinin titer at bx	32 (IgM) 256 (IgG)	8 (IgM) 16 (IgG) 128 (IgG at 3 wk post-OP)	1 (IgM) 2 (IgG)	32 (IgM) 256 (IgG)
HLA Ab at bx	PRA negative	PRA negative	Class II	PRA negative
Bile duct injury	Yes	NA	Yes	NA
Ductular reaction	Yes	Yes	NA	Yes
Periportal inflammation	Yes	Yes	NA	Yes
Endothelitis	No	Yes	NA	Yes
Microvasculitis	Yes	NA	No	NA
C4d	20%	10%	Equivocal	<50%
Status	Expired	Re-transplant	Re-transplant	Alive

bx = biopsy; BSA = body surface area; DIC = diffuse intrahepatic cholangiopathy; HLA = human leukocyte antigen; LDLT = living donor liver transplant; NA = not available; OP = operation; POD = postoperative days; PRA = panel reactive antibody.

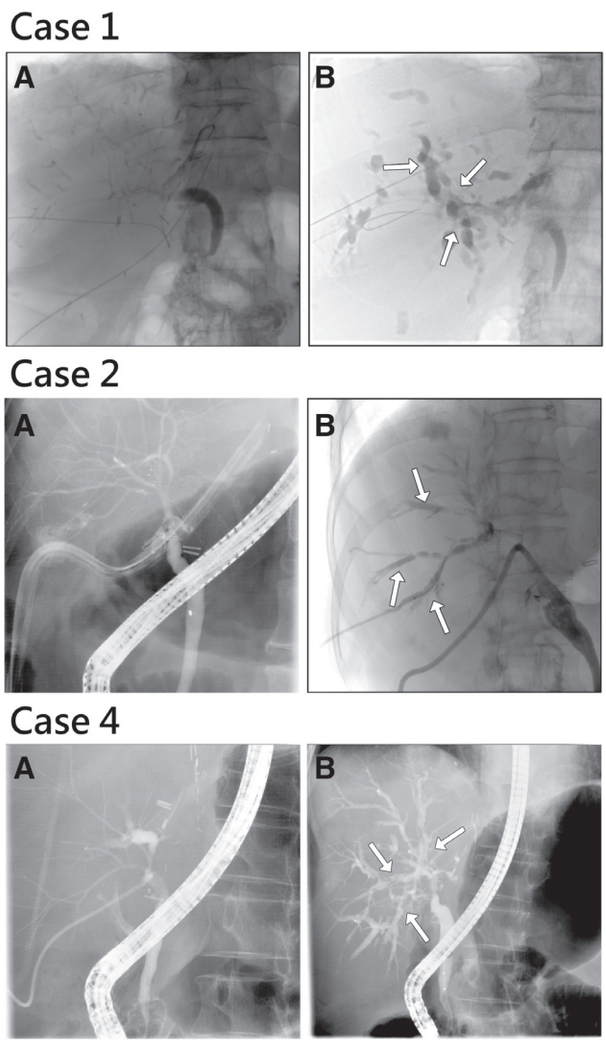


Fig. 3 ERCP of the 3 patients (case 1, case 2, and case 4 from upper to lower) before and after the onset of DIC. Case 1: A, ERCP before the onset of DIC (1 mo post-LDLT). B, ERCP after the onset of DIC (3 mo post-LDLT). Case 2: A, ERCP before the onset of DIC (3 wk post-LDLT). B, ERCP after the onset of DIC (4 mo post-LDLT). Case 4: A, ERCP before the onset of DIC (3 wk post-LDLT). B, ERCP after the onset of DIC (2.5 mo post-LDLT). White arrows indicate stricture of IHDs. DIC = diffuse intrahepatic cholangiopathy; ERCP = endoscopic retrograde cholangiopancreatography; IHD = intrahepatic duct; LDLT = living donor liver transplant.

explain these outcomes. The combination of other potent immunosuppressive agents, such as T-cell inactivation or plasma cell apoptosis agents, and the early recognition of antibody rebound to initiate salvage treatment may improve long-term outcomes among these patients.

ACKNOWLEDGMENTS

The authors thank all of their colleagues who contributed to this study. The authors are grateful to the Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital and medical technologist Ying-Ju Chen for providing detailed information about the lymphocyte surface markers and isoagglutinin antibody titer testing method. In addition, we would like to thank our research assistants, Chia-Pei Liu and Li-Yang Lai, who assisted with project application and the organization of patient data; we express our gratitude to coordinators Li-Feng Liao, Zih-Yu Lin; Ya-Lin Huang, Ching-Yen Wang, Yu-Ping Tsai, Jui-Chen Chong, and Ju-Hsin Chang for assisting in the preservation and provision of medical records. Finally, we extend our gratitude to the Hsiang Shan Medical Charity Foundation for their support in this study. Our research was approved by the Institutional Review Board, Taipei Veterans General Hospital (number 2024-03-016AC), and written consent was given by all subjects.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A308.

REFERENCES

1. Human Organ Transplant. *Laws & Regulations Database of The Republic of China (Taiwan)* 2021.
2. Tanabe M, Shimazu M, Wakabayashi G, Hoshino K, Kawachi S, Kadomura T, et al. Intraportal infusion therapy as a novel approach to adult ABO-incompatible liver transplantation. *Transplantation* 2002;73:1959–61.
3. Nakamura Y, Matsuno N, Iwamoto H, Yokoyama T, Kuzuoka K, Kihara Y, et al. Successful case of adult ABO-incompatible liver transplantation: beneficial effects of intrahepatic artery infusion therapy: a case report. *Transplant Proc* 2004;36:2269–73.
4. Egawa H, Teramukai S, Haga H, Tanabe M, Fukushima M, Shimazu M. Present status of ABO-incompatible living donor liver transplantation in Japan. *Hepatology* 2008;47:143–52.
5. Song GW, Lee SG, Hwang S, Kim KH, Ahn CS, Moon DB, et al. ABO-Incompatible adult living donor liver transplantation under the desensitization protocol with rituximab. *Am J Transplant* 2016;16:157–70.
6. Kim SH, Lee EC, Shim JR, Park SJ. A simplified protocol using rituximab and immunoglobulin for ABO-incompatible low-titre living donor liver transplantation. *Liver Int* 2018;38:932–9.
7. Shen T, Lin BY, Jia JJ, Wang ZY, Wang L, Ling Q, et al. A modified protocol witrituximab and intravenous immunoglobulin in emergent ABO-incompatible liver transplantation for acute liver failure. *Hepatobiliary Pancreat Dis Int* 2014;13:395–401.
8. Lee B, Cho JY, Han HS, Yoon YS, Lee HW, Lee JS, et al. Long-term outcomes of emergency ABO-incompatible living donor liver transplantation using a modified desensitization protocol for highly sensitized patients with acute liver failure: a case report. *Ann Hepatobiliary Pancreat Surg* 2021;25:571–4.
9. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. *Semin Liver Dis* 1986;6:97–106.
10. Gugenheim J, Samuel D, Reynes M, Bismuth H. Liver transplantation across ABO blood group barriers. *Lancet* 1990;336:519–23.
11. Yadav DK, Hua YF, Bai X, Lou J, Que R, Gao S, et al. ABO-Incompatible adult living donor liver transplantation in the era of rituximab: a systematic review and meta-analysis. *Gastroenterol Res Pract* 2019;2019:8589402.
12. Monson NL, Cravens PD, Frohman EM, Hawker K, Racke MK. Effect of rituximab on the peripheral blood and cerebrospinal fluid B cells in patients with primary progressive multiple sclerosis. *Arch Neurol* 2005;62:258–64.
13. Jones JD, Hamilton BJ, Rigby WF. Rituximab mediates loss of CD19 on B cells in the absence of cell death. *Arthritis Rheum* 2012;64:3111–8.
14. Egawa H, Ohdan H, Saito K. Current Status of ABO-incompatible liver transplantation. *Transplantation* 2023;107:313–25.
15. Lee CF, Cheng CH, Wang YC, Soong RS, Wu TH, Chou HS, et al. Adult living donor liver transplantation across ABO-incompatibility. *Medicine (Baltim)* 2015;94:e1796.
16. Hsu SC, Thorat A, Jeng LB, Li PC, Chen TH, Yang HR, et al. ABO-incompatible living donor liver transplantation with reduced rituximab dose: a retrospective analysis of 65 patients—can we fast-track liver transplant surgery and improve long-term survival? *Ann Transplant* 2020;25:e923502.

17. Nakanuma Y, Sasaki M. Expression of blood group-related antigens in the intrahepatic biliary tree and hepatocytes in normal livers and various hepatobiliary diseases. *Hepatology* 1989;10:174–8.
18. Okada Y, Jinno K, Moriwaki S, Shimoe T, Tsuji T, Murakami M, et al. Blood group antigens in the intrahepatic biliary tree. I. Distribution in the normal liver. *J Hepatol* 1988;6:63–70.
19. Lee WC, Cheng CH, Lee CF, Hung HC, Lee JC, Wu TH, et al. Quick preparation of ABO-incompatible living donor liver transplantation for acute liver failure. *Clin Transplant* 2022;36:e14555.
20. Kovarik J, Breidenbach T, Gerbeau C, Korn A, Schmidt AG, Nashan B. Disposition and immunodynamics of basiliximab in liver allograft recipients. *Clin Pharmacol Ther* 1998;64:66–72.
21. Lemy A, Toungouz M, Abramowicz DB. A new player in pre- and post-transplant desensitization? *Nephrol Dial Transplant* 2010;25:3480–9.
22. Natsuda K, Murokawa T, Lee KW, Yoon KC, Hong SK, Lee JM, et al. No diffuse intrahepatic biliary stricture after ABO-incompatible adult living donor liver transplantation using tailored rituximab-based desensitization protocol. *Ann Transl Med* 2021;9:30.