Review

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Current Status of ABO-incompatible Liver Transplantation

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Abstract. By 2014, strategies to prevent antibody-mediated rejection (AMR) after ABO-incompatible (ABO-I) living donor liver transplantation (LDLT) were established in Japan and expanded primarily to Asia, where LDLT is now the predominant form of LT owing to the scarcity of brain-dead donors. A desensitization protocol consisting of rituximab (375 mg/m^2), plasma pheresis, tacrolimus, and mycophenolate mofetil before LDLT, followed by standard immunosuppression, is currently the best option in terms of safety and efficacy. Rituximab administration is now known not to increase the risk of hepatocellular carcinoma recurrence, and the feasibility of rituximab for LDLT for acute liver failure and the need for desensitization before LDLT in children older than 1 y have been documented. Strategies are needed to distinguish patients at high risk of AMR from those at low risk and to adjust immunosuppression to prevent both AMR and infection. Specific single-nucleotide polymorphisms in genes encoding Fcγ receptors affecting the cytotoxicity of rituximab on B cells could be useful for adjusting immunosuppression levels to decrease infectious complications. Immunological accommodation after ABO-I transplantation could be provided by immune factors in both the grafts and recipients.

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INTRODUCTION

ABO-incompatible (ABO-I) liver transplantation (LT) is an alternative to ABO-compatible living-donor liver transplantation (LDLT). Increases in the safety of ABO-I LDLT, primarily due to effective desensitizing protocols that prevent antibody-mediated graft rejection (AMR) in recipients, have widened the pool of patients eligible to receive this therapy. The ABO barrier in kidney transplantation (KT) fell rapidly thanks to Professor Alexandre's pioneering efforts.[1] However, considering the miserable outcomes of liver transplantation in general, ABO-I liver transplantation (LT) was initially limited to highly select patients.[2] LDLT began in 1996 in Japan, where many technical innovations were accomplished. Strategies to prevent AMR after ABO-I LDLT were established in Japan in 2014 and then expanded primarily to Asia, where LDLT is the predominant form of LT owing to the scarcity of brain-dead donors and where ABO-I now accounts for approximately 20% of all LDLT procedures. Thereafter, in Korea, the number of ABO-I LTs increased dramatically, revealing that rituximab administration was not a risk factor for the recurrence of hepatocellular carcinoma and prompting center-wise modification of the rituximab-based regimen.

In this overview, we first summarize (1) the mechanisms and pathology of AMR after ABO-I LT and (2) fundamental information for clinical practice. Then, we discuss (3) current immunosuppression protocols for ABO-I LDLT, and their modification (4) specific patient populations, (5) address mechanisms involved in desensitization with rituximab and accomodation, and finally (6) note future challenges.

MECHANISMS AND PATHOLOGY OF AMR AFTER ABO-I LT

Mechanism of ABO-I–related AMR

All people have preformed antibodies against A and B blood-type antigens that they do not express; these antigens are carbohydrates, and the presentation of these antigens in the context of ABO-I transplantation induces a strong antibody-mediated response that can lead to AMR. ABO blood-type antigens are expressed on the surfaces of red blood cells and biliary and vascular epithelia,[3] and antibodies bind to these surface antigens. In addition, complement binds to Fc receptors, leading to activation

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of the complement cascade (Figure 1). In the phenomenon known as disseminated intravascular coagulation, the resulting inflammatory reaction destroys the capillary epithelium and develops small thrombi in the injured epithelium impairs blood circulation (Figure 1).

The pathogenesis of thrombotic microangiopathy in disseminated intravascular coagulation can explain the mechanisms of AMR after LDLT. The major links between inflammatory cytokines and microvascular thrombosis involve the activation of coagulation, inhibition of anticoagulation pathways, and depression of fibrinolysis.[4] In particular, Kupffer cells activated by complement-dependent cytotoxicity in the liver graft secrete interleukin (IL) 6, IL1β, and tumor necrosis factor-alpha (TNFα), which regulate the process of microvascular thrombosis (Figure 1).[5] Adhesion molecules mediate the interaction between neutrophils and the endothelium, and between platelets and the endothelium. TNF and IL1 can initiate the synthesis and expression of E-selectin or the rapid expression of P-selectin on the endothelium.[6] After adherence, neutrophils secrete several enzymes that cause endothelial activation or injury.[7] Activation of endothelial cells results in a thrombogenic phenotype, in which the levels of thrombomodulin and endothelial protein C receptor are downregulated, whereas the expression and secretion of plasminogen activator inhibitor 1 and von Willebrand factor are induced.[4] P-selectin accelerates thrombosis through platelet-endothelial activation and their cellular interaction.[8] Microparticles bearing these various tissue factors and arising from leukocytes fuse with the membranes of activated platelets, thereby localizing these factors to the platelet surfaces. In addition, von Willebrand factor contributes to the adherence of activated platelets to the subendothelium in regions of high shear stress, and clotting factors bind to receptors on adherent and activated platelets, thereby localizing at the site of injury all of the factors needed for hemostasis.

The complex series of reactions leading to thrombin generation requires the positioning of each coagulation protein close to its activating protease. Factor VIIa activates factor X; factor Xa activates factor V; prothrombin activates factors V, VIII, and XI; and factor XIa activates factor IX. Activated coagulation factors within the developing thrombus are protected from inactivation by circulating protease inhibitors.[9]

This circulatory disturbance occurs within 14 d after transplantation and leads to liver necrosis (Figure 2, left) or intrahepatic biliary destruction (Figure 2, right), or both. When these circulatory disturbances are limited to small arteries only, diffuse intrahepatic cholangitis and sclerosis develop; when circulatory disturbances are massive, hepatic necrosis occurs.[3] Liver necrosis manifests within 1 mo after transplantation and intrahepatic biliary complication (IHBC) between 1 and 3 mo afterward.[10,11] A syndrome of "ABO-I–related chronic AMR" in ABO-I LT has not been reported to date.

Diagnosis of Graft Rejection in ABO-I LDLT: Pathology

In a Japanese multicenter study involving 259 patients who received rituximab prophylaxis, the incidence of acute cellular rejection was 26%; that of chronic rejection was 1.4%, and that of AMR was 5.8%.[12] In a Korean single-center study that compared patients treated with ABO-I after rituximab prophylaxis (n = 235) and those who underwent ABO-compatible (ABO-C) transplantation (n = 1301), the incidences of acute cellular rejection were 8.1% and 9.4%, of chronic rejection were 0.9% and 0.9%, and of AMR leading to diffuse intrahepatic cholangitis were 7.2% and 0%, respectively.[13] Therefore, the incidences of acute cellular rejection and chronic rejection did not differ between ABO-I and ABO-C transplantations.[13]

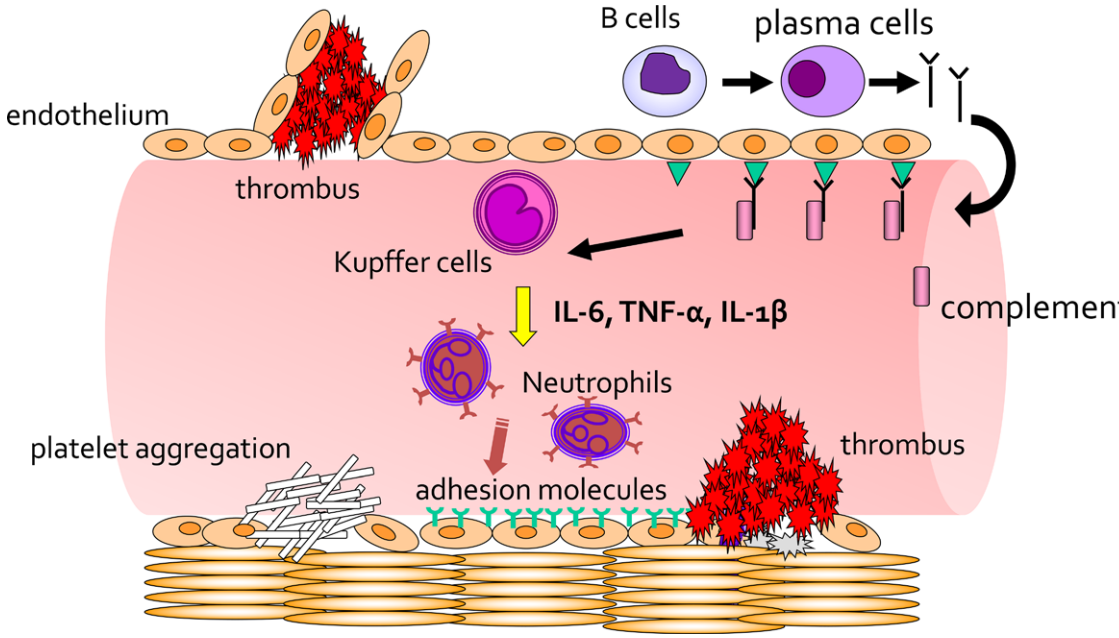

FIGURE 1. Mechanism of antibody-mediated rejection. Antibodies bind to antigens on the surface of the vascular epithelium and complement binds to Fcγ receptors, leading to activation of the complement cascade. The resulting inflammatory reaction destroys the capillary epithelium, and small thrombi develop and impair blood circulation. IL-1β, interleukin 1β; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha.

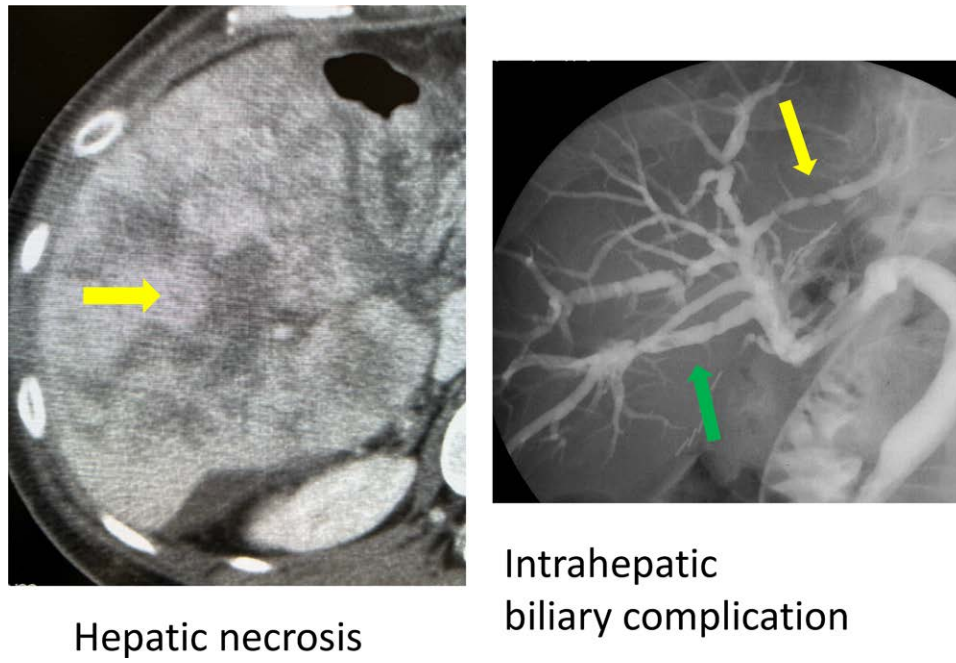

FIGURE 2. Radiologic features of ABO-I–related antibody-mediated rejection. Left panel: The low-density area (arrow) is a necrotic area in the liver. Right panel: This cholangiographic image reveals intrahepatic biliary complications, including segmental stenosis (yellow arrow) and dilatation (green arrow) of intrahepatic bile ducts. ABO-I, ABO-incompatible.

In 2004, Haga et al reported portal edema and necrosis as an important early finding of ABO-I-related AMR (Figure 3, left), and in 2006 they reported the usefulness of monitoring C4d deposition during ABO-I-related AMR in LDLT (Figure 3, right).[14,15] The edematous appearance of these portal areas results primarily from the obstruction of sinusoids with fibrinous deposition rather than from direct injury. However, the addition of periportal hemorrhage as well as disarray or necrosis of hepatocytes around the portal tracts to the early-onset edema indicates destruction of the periportal structure to varying degrees.[14] When the inflammation after LDLT is not controlled, small thrombi develop, first in small arteries and progressing to the sinusoids, thus causing liver necrosis, IHBC, or both (Figure 4). Figure 5 shows arterial inflammation in the explanted liver of a patient who developed IHBC, and intimal hypertrophy of an artery in the explanted liver in a patient who developed hepatic necrosis. These findings suggest that various vasculopathies contribute to the development of AMR after ABO-I LDLT.

Before the use of rituximab, postoperative increases in isoagglutinin were often associated with fatal AMR, which was characterized by periportal edema, necrosis, and hemorrhage.[14,15] In addition, C4d deposition was commonly seen in the portal stroma and endothelium. In contrast, in ABO-I transplant recipients treated with preoperative rituximab as well as plasmapheresis or blood exchange, most of the C4d-positive ABO-I patients had low anti-A/B antibody titers at the time of biopsy and lacked histologic evidence of critical graft injury.[16] In other words, in the rituximab era, C4d positivity without an elevation in anti-donor A/B antibodies is not uncommon among patients with ABO-I LT.[16] This scenario is somewhat similar to the findings in ABO-I

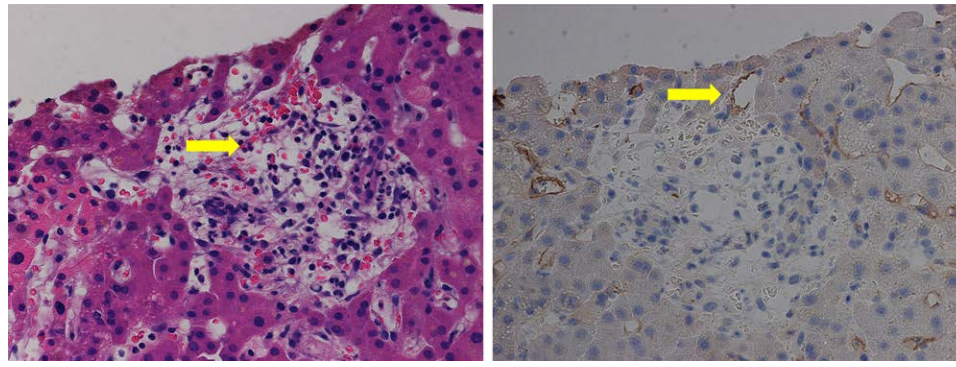

FIGURE 3. Pathologic findings of early antibody-mediated rejection after liver transplantation. This 30-y-old woman was diagnosed with primary sclerosing cholangitis and was scheduled to undergo ABO-I LDLT. After she received 500 mg of rituximab, her surgery was postponed for 1 mo because of the COVID-19 pandemic. One week before transplantation, her $CD19^+$ B-cell frequency was 2%. She underwent LDLT without additional administration of rituximab. She developed a high fever and increased C-reactive protein level on postoperative day (POD) 5 and underwent liver biopsy for pathological diagnosis on POD7. The image on the left shows periportal edema and necrosis in the portal area. The right panel shows C4d deposition along sinusoids. Both of these signs are indicative of antibody-mediated transplant rejection. ABO-I, ABO-incompatible; LDLT, living-donor liver transplantation.

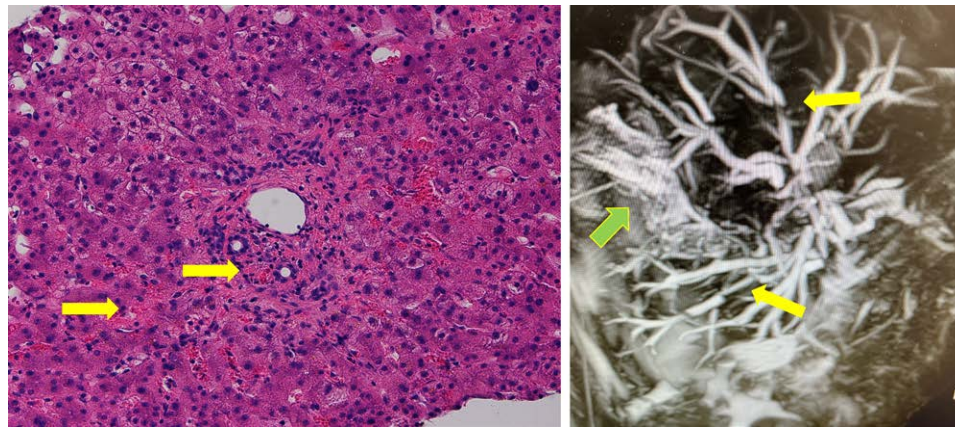

FIGURE 4. Pathologic features of antibody-mediated rejection after liver transplantation. This patient is the same as in Figure 3. The left image is of a liver specimen obtained on POD 14 and shows the development of small thrombi (arrows) that occupy the small arteries to sinusoids. By POD 30, the patient had developed multiple areas of liver necrosis (see Figure 2, left). The right image was obtained through magnetic resonance cholangiography 6 mo after transplantation. The patient had developed a liver abscess (green arrow indicates abscess wall) and multiple intrahepatic biliary stenoses (yellow arrows). To resolve these complications, she underwent retransplantation using the left liver lobe from her 67-y-old father. POD, postoperative day.

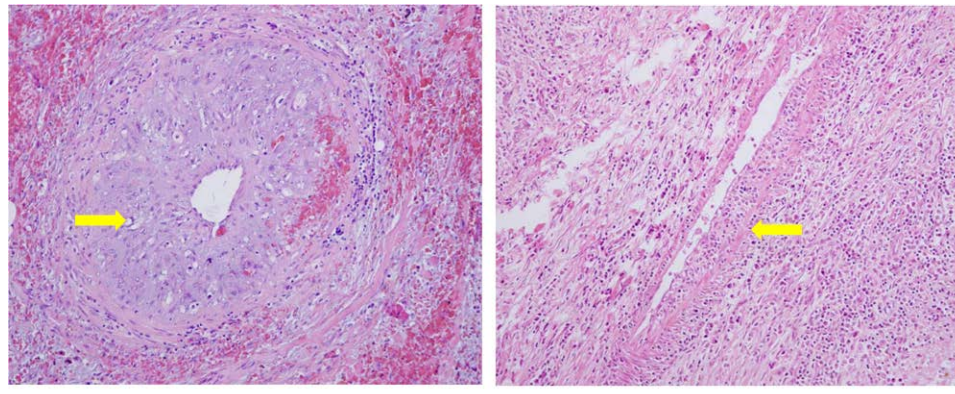

FIGURE 5. Vasculopathy of the hepatic arteries of failed grafts secondary to antibody-mediated rejection after ABO-I LDLT. The left image shows intimal hypertrophy (arrow) of the artery in the explanted liver of a patient who developed hepatic necrosis. The right image shows inflammation of the artery (arrow) in the explanted liver of a patient with intrahepatic biliary complications. ABO-I, ABO-incompatible; LDLT, living-donor liver transplantation.

kidney allografts.[17] As applied in ABO-I renal transplantation, monitoring of the postoperative titers of anti-donor A/B antibodies may be a practical method for predicting acute AMR in patients undergoing ABO-I LDLT, thus rendering C4d immunostaining unnecessary as a routine diagnostic method. However, C4d immunostaining remains a viable means for confirming the presence of AMR.

FUNDAMENTAL INFORMATION FOR CLINICAL PRACTICE

Immunosuppression

Splenectomy

Because the spleen is considered the site of B-cell maturation and antibody production, splenectomy has been an integral part of the protocol for ABO-I LT at many centers.[18,19] However, preoperative rituximab effectively decreases anti-ABO antibody levels sufficiently to prevent AMR, such that splenectomy may not yield any immunological benefit in ABO-I LT with preoperative rituximab administration.[20]

Plasma Exchange

Plasma exchange (PE) with fresh-frozen AB plasma is the fundamental method for decreasing isoagglutinin titers. The targeted isoagglutinin titer ranges from 1:8 to 1:16.[13,16] The frequency and timing of PE events vary depending on the center and the individual patient. When isoagglutinin titers increase after transplantation, PE is the only method available for decreasing the titer mechanically, and titer rebound necessitates additional PE.

Hepatic Infusion Therapy

A particular clinical achievement regarding ABO-I LDLT was the discovery of the beneficial effect of portal infusion treatment (PVI), which helped to increase the survival rate after adult ABO-I LDLT in Japan from 20% to 60%.[21] This favorable result led to the inclusion of hepatic arterial infusion therapy (HAI) in LDLT protocols.[22] PVI was introduced in 2000, HAI combined with PVI in 2001, and HAI without PVI in 2003.

During PVI, prostaglandin E1 (PgE1), methylprednisolone, and mesylates (or an analog) were administered through a catheter into the portal vein for 3 wk after

transplantation.[21] For HAI, PgE1, and steroids ABO-I, ABO-incompatible were administered through a catheter into the hepatic artery.[22] In HAI with PVI, PgE1, and steroids were administered through a catheter into the hepatic artery and mesylates through a catheter into the portal vein. For local infusion therapy, PgE1 (0.01 μg/kg/min) and methylprednisolone (100 mg daily) are continuously administered through a catheter for 3 wk.

In a Japanese multicenter study, the incidence of catheter-related complications was 37% in PVI (7 cases of portal vein thrombosis, 5 of sepsis, 2 of accidental catheter dislocation, and 1 of hepatic embolism), 22% during PVI with HAI (1 case each of superior mesenteric vein thrombosis, hepatic artery thrombosis, and bleeding of the hepatic artery, and 2 cases of accidental dislocations), and 16% for HAI (7 cases of hepatic artery bleeding and 1 of accidental catheter dislocation).[4] Although the incidence of catheter-related complications was lower during HAI, the complications were more severe than for other protocols.[10]

IVIG

Ikegami et al reported a protocol consisting of rituximab and high-dose IVIG without hepatic infusion.[23] In the field of kidney transplantation, the use of IVIG to control acute humoral rejection in highly sensitized candidates has been effective.[24-26] The proposed mechanisms of action of IVIG in humoral rejection include the apoptosis of B cells or plasma cells through the Fc receptor-dependent pathway and the inhibition of alloreactive T cell– or complement-mediated allograft injury.[24-26]

B Cell-targeted Strategy

Additional landmark contributions from a follow-up cohort study involved insights into B cell dynamics after LT with or without rituximab to combat AMR, the importance of the timing of rituximab administration, and the possible contribution of memory B cells during AMR.[27] The Japanese Society for ABO-I Kidney and Liver Transplantation collected clinical data prospectively to evaluate the effect of rituximab in the context of LDLT. These experiences led to the implementation of a standardized protocol in 2008 for the use of rituximab for LDLT in Japan.[10] This first protocol underwent several minor revisions, which culminated (in 2014) in the current protocol (Figure 6).[12] The minimal amount of rituximab needed to prevent AMR was reported in 2017.[28]

CURRENT IMMUNOSUPPRESSION PROTOCOLS FOR ABO-I LDLT, AND THEIR MODIFICATION

Current Immunosuppression Protocols

In the standard protocol, rituximab (375 mg/m^2) is administered for 2 wk before transplantation; additional doses are considered in light of the patient's condition when B-cell depletion is insufficient (greater than 1% of the initial count). To assess the B-cell population, the CD19$^+$ (rather than CD20$^+$) mononuclear cell count is obtained before the administration of rituximab, at 2–3 and 5–7 d after administration, immediately before transplantation, and once a month after transplantation until the B-cell number recovers. In addition, tacrolimus and mycophenolate mofetil (MMF) are started 7 d before transplantation, because tacrolimus delays B1-cell proliferation in mice[29]; the trough tacrolimus level is adjusted to approximately 5 ng/mL. MMF is initiated at a dose of 500 mg daily and, when tolerated, is increased to 1000 mg daily. Patients whose isoagglutinin titers are greater than 1:256 or 1:512 undergo 2 or 3 sessions of PE immediately before transplantation.

For monitoring specific to ABO-I LDLT, isoagglutinin titers are measured daily during the first 2 wk after transplantation and then twice weekly during the next 2 wk. Isoagglutinin immunoglobulin G (IgG) and IgM titers should both be measured.

To prevent infections secondary to hypogammaglobulinemia, the serum IgG level should be monitored until it recovers.

The standard immunosuppressive protocol for ABO-I LDLT avoids the need for splenectomy and local infusion. In addition, induction with anti-T cells or IL2 receptor antibodies is not part of the standard preparatory protocol for LT. In ABO-I kidney transplantation, the inclusion of T cell-targeted induction treatment enables the use of a much smaller rituximab dose than for ABO-I LT.[30] The minimal safe dose of rituximab for use with T cell-targeted induction during LT is unknown as yet.

Modifications

Two single-center studies from Japan confirmed the safety and efficacy of rituximab monotherapy and the elimination of preoperative PE.[31,32] In another trial, the standard rituximab dose (375 mg/m^2) was decreased to 200 mg/m^2. The patients also received 4 sessions of

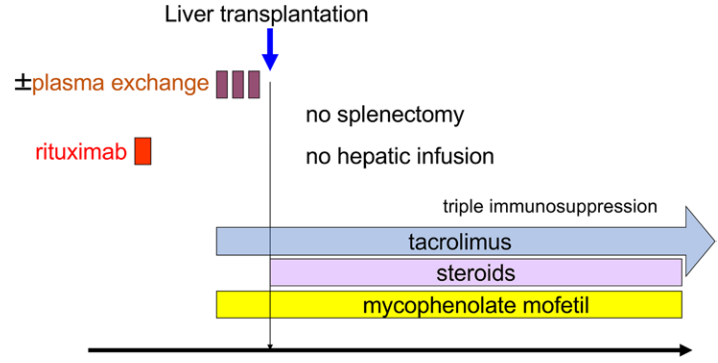

FIGURE 6. Current standard protocol for ABO-I LT. The current protocol for ABO-I LT includes rituximab (375 mg/m^2) at 2 wk before LT, tacrolimus, and mycophenolate mofetil for 7 d just before LT, no splenectomy, no hepatic infusion, and triple immunosuppression, with the addition of plasma exchange for patients with high hemagglutinin titers. ABO-I, ABO-incompatible; LT, liver transplantation.

double-filtration plasmapheresis before transplantation, and basiliximab, tacrolimus, everolimus, intravenous corticosteroids, and MMF after transplantation. Fatal infection occurred in 10% of the recipients, and intrahepatic biliary complications in 8%.[33] In this context, rituximab at 200 mg/m^2 was insufficient for desensitization. Furthermore, extreme immunosuppression—due to an increase in the amount and number of immunosuppression drugs other than rituximab to compensate for inadequate B-cell depletion—led to the fatal infections.[28]

However, even at a rituximab dose of 375 mg/m^2, the incidence of intrahepatic biliary complications related to AMR is still 5%.[34] The rituximab dose needs to be minimized to prevent infectious complications, but patients at high risk of AMR require additional desensitization. In one counterstrategy, when the ABO isoagglutinin titer exceeded 1:16 just before LT and after plasma exchange, high-dose IVIG (0.8 g/kg daily) was administered for 5 d beginning on postoperative day 1; concurrent splenectomy was added selectively.[35] However, in the era of rituximab desensitization, the value of the preoperative isoagglutinin titer has become unclear,[34] and a prospective study is warranted.

Another group assessed the efficacy of a plasma treatment procedure comprising PE and immunoadsorption in the absence of rituximab.[36] The study involved 10 patients with hepatocellular carcinoma (HCC), from among whom 6 were selected according to the decrease in hemagglutinin titers after PE. Patients whose titers rebounded after transplantation received 1 to 12 rounds of PE, tacrolimus, and MMF for 3 d before transplantation, basiliximab on day 2 after transplantation, and iloprost (a prostaglandin I2 receptor agonist) for 10 d after transplantation; 1 patient died from severe AMR.[36]

SPECIFIC PATIENT POPULATIONS

This section of our overview focuses on 4 current questions regarding ABO-I LDLT: (1) the effect of rituximab during ABO-I LDLT for patients with HCC, (2) the feasibility of rituximab for ABO-I LDLT indicated for acute liver failure (ALF), (3) pediatric LDLT, and (4) new complications of ABO-I LDLT.

Effect of Rituximab During LDLT for Patients With HCC

A 2015 report from Korea reported a tendency for early tumor recurrence in patients who received ABO-I LDLT for advanced HCC: 5 of the 15 patients (33.3%) experienced early tumor recurrence (1 of 8 within Milan criteria and 4 of 7 beyond).[37] In contrast to the 2015 findings, all other reports published after 2018 showed no difference in disease-free survival between ABO-I LT with rituximab and ABO-C LT. For example, a comparison of 165 ABO-I LDLT recipients and 165 propensity-score–matched ABO-C patients showed that ABO incompatibility was not a risk factor for HCC recurrence despite rituximab desensitization.[38] An evaluation of 51 ABO-I and 181 ABO-C procedures found no difference in patient survival or HCC recurrence between the groups.[39] These results were confirmed in a study that compared 39 ABO-I and 78 ABO-C patients selected by propensity score matching.[40] Note that, in these 3 studies, neither overall or disease-free survival differed, regardless of whether disease scoring was within or beyond the Milan criteria classification (Table 1).[38-40]

Feasibility of Rituximab for ABO-I LDLT Indicated for ALF

A Japanese multicenter study reported no AMR or mortality among 6 patients treated with rituximab immediately before ABO-I LDLT for ALF.[12] However, all 6 patients received additional desensitization measures, such as splenectomy (n = 4) and hepatic infusion (n = 5), as well as PE using blood-type AB fresh-frozen plasma followed by rituximab administration.[12]

In 2021, the feasibility of rituximab was addressed in 1 publication each from Taiwan and Korea.[41,42] The first focused on 8 patients treated with bortezomib and

TABLE 1.

Summary of reports of effects of rituximab on outcomes of liver transplantation for hepatocellular carcinoma

Authors	Yoon et al	Kim et al	Kim et al
Reference	31	32	33
No. patients (ABO-I: ABO-C)			
	165:753	59:181	39:78
Rituximab dose	375 or 300 mg/m^2	375 mg/m^2	300 mg/m^2
Basiliximab	None	All patients	All patients
Positive HBV (ABO-I:ABO-C)			
	139 (84%):635 (84%)	147 (81%):54 (92%)	33 (84%):65 (83%)
No. patients with disease beyond Milan criteria (ABO-I: ABO-C)			
	29 (18%):206 (27%)	50 (28%):16 (27%)	19 (48%):38 (49%)
Overall survival (%; 1,3, 5 y) (ABO-I:ABO-C)			
Entire cohort	96, 89, 86:96, 86, 81	71, 82, 80:88, 83, 80	82, 73, 73:82, 80, 80
Within Milan	not available	not available	90,85,85: 94, 90, 90
Beyond Milan	83, 71, 66:95, 77, 66	Not available	65,58,58:80, 72, 72
Disease-free survival (%; 1, 3, 5 y) (ABO-I:ABO-C)			
Entire cohort	91, 86, 82:90, 83, 81	91, 73, 70:87, 75, 71	77, 69, 64:74, 71, 71
Within Milan	Not available	95, 85, 80:90, 80, 73	100, 97, -:80, 78, 75
Beyond Milan	68, 59, 59:82, 66, 63	67, 0, 0:68, 58, 58	51, 37, 37:54, 52, 52

ABO-C, ABO-compatible; ABO-I, ABO-incompatible.

PE before transplantation and given rituximab postoperatively; 1 patient developed fatal AMR.[41] In the other publication, a case report, rituximab (375 mg/m^2) was administered 3 d before LT, and IVIG (0.8 g/kg) was infused, beginning on the day of LT during the anhepatic phase and continuing until 3 d after transplantation.[42] Although the patient's baseline isoagglutinin antibody titer was high (1:1024) and her panel reactive antibody was 100% positive before transplantation, she did not undergo plasmapheresis. Despite acute cellular rejection, the patient maintained stable graft function for >5 y. Although we still have little experience with this treatment scenario, patients receiving ABO-I LDLT for ALF are recommended to receive a full desensitization protocol consisting of pretransplantation rituximab (375 mg/m^2) regardless of time until surgery, PE using blood-type AB fresh-frozen plasma, splenectomy, and IVIG for 3 to 5 d.

Pediatric ABO-I LDLT

In Japan, ABO-I LDLT began in young children and progressively expanded to include older recipients. A key obstacle to the success of ABO-I LDLT in children is the need to counter AMR. The first ABO-I LDLT pediatric cohort study revealed the profound effect of age on the incidence and severity of AMR.[43] Before the introduction of rituximab, pediatric recipients—like their adult counterparts—developed fatal AMR leading to massive hepatic necrosis or extensive intrahepatic biliary tract destruction and sclerosis, at rates of 37% (10 of 27) in children 8 to 15 y old and 21.7% (13 of 60) in children 1 to 7 y old.[43] In contrast, the incidence of AMR in children younger than 1 y was 1% (1 of 68) in that cohort.[43]

To prevent these life-threatening complications, one group recommended extending the desensitization protocol with rituximab to include children older than 1 y[44]; other investigators have reported a stepwise strategy based on isoagglutinin titers for children older than 1 y.[45] According to which C4d immunostaining was considered to be a hallmark of acute humoral rejection in ABO-I LT, children whose pretransplantation titers were 1:16 or greater received 375 mg/m^2 rituximab on day 14 before LT, and those whose titers remained 1:16 or greater on day 7 before transplantation underwent plasmapheresis. When isoagglutinin remained at 1:16 or greater on day 5 before transplantation, patients received IVIG treatment (100 mg/kg) and the second round of plasmapheresis. Finally, additional plasmapheresis was performed on day 1 before ABO-I LT when isoagglutinin titers remained at 1:16 or higher despite the previous preparation protocol.[45]

The report on the 20-y experience of the TRANSPLANT-CHILD European Reference Network[46] included 142 patients who underwent LDLT between 1986 and 2018 at 8 European transplant centers. Before ABO-I LT, pre transplantation desensitization of children was very uncommon at European centers, with high-dose IVIG being administered more often than other alternatives, but only in 8% of recipients. Diffuse intrahepatic biliary stenosis occurred significantly ($P < 0.05$) more often in children older than 1 y and was recognized only in patients transplanted before 2011. In addition, the overall patient outcomes were significantly better after 2011 than before. In particular, patient mortality after 2011 (19%) was significantly lower ($P < 0.05$) than that before 2011 (33%). However, mortality was higher in the TRANSPLANT-CHILD patient cohort[46] than in others.[44,45]

New Complications Associated With ABO-I LDLT

AMR and infections are the most common complications of ABO-I LDLT. In a recent report, high preoperative initial and postoperative peak IgM isoagglutinin titers were significantly associated with the development of acute kidney injury, although the causal relationship between high isoagglutinin titers and the risk of acute kidney injury was unclear.[47] High baseline and postoperative isoagglutinin titers might be simple warning signs of the risk of acute kidney injury after ABO-I LDLT.

In another study cohort, the incidence of systemic thrombotic microangiopathy was 10.1% overall but was especially high (37.9%) among cases of ABO-I LT.[48] Univariate analysis revealed that ABO incompatibility, use of tacrolimus, use of rituximab, and cold ischemic time of 350 min were risk factors for systemic thrombotic microangiopathy ($P < 0.10$). Multivariate analysis demonstrated that ABO incompatibility was the only independent risk factor for systemic thrombotic microangiopathy ($P = 0.009$). Initiating treatment consisting of calcineurin inhibitor dose reduction or fresh frozen plasma administration, or both, on the day of diagnosis is associated with better survival.[48]

MECHANISMS INVOLVED IN DESENSITIZATION WITH RITUXIMAB AND ACCOMODATION

This section of our overview focuses on 2 basic aspects of ABO-I transplantation: (1) mechanisms of B-cell depletion by rituximab and the role of gene polymorphism, and (2) mechanisms of accommodation.

Mechanisms of B-cell Depletion by Rituximab and Significance of Gene Polymorphisms

Mechanism of B-cell Depletion by Rituximab

Incorporating rituximab into the desensitization protocol for LDLT has significantly reduced the incidence of AMR and improved the outcome of adult ABO-I LDLT.[10] Rituximab, a human-murine chimeric anti-CD20 Ig G1 monoclonal antibody, is used to eliminate or reduce the quantities of plasma cell precursors and plasma B cells responsible for producing antibodies targeting the blood-group carbohydrates expressed on ABO-I allografts. Several mechanisms are thought to be involved in the elimination of CD20$^+$ cells by rituximab (Figure 7).[49]

Complement-dependent cytotoxicity is the mechanism by which antibody-coated target cells recruit and activate components of the complement cascade. Antibodies—mostly IgG1 and IgG3—elicit complement-dependent cytotoxicity by binding their Fc region to serum complement components, particularly C1q. Complicated enzyme activation and cleavage events eventually lead to the formation of a membrane-attacking complex and subsequent cell lysis. Hence, complements may play a role in the clinical response to rituximab and other monoclonal antibody-based therapies. Patients with liver failure who require LT typically have decreased levels of complement factors, which are synthesized mainly in the liver. This situation

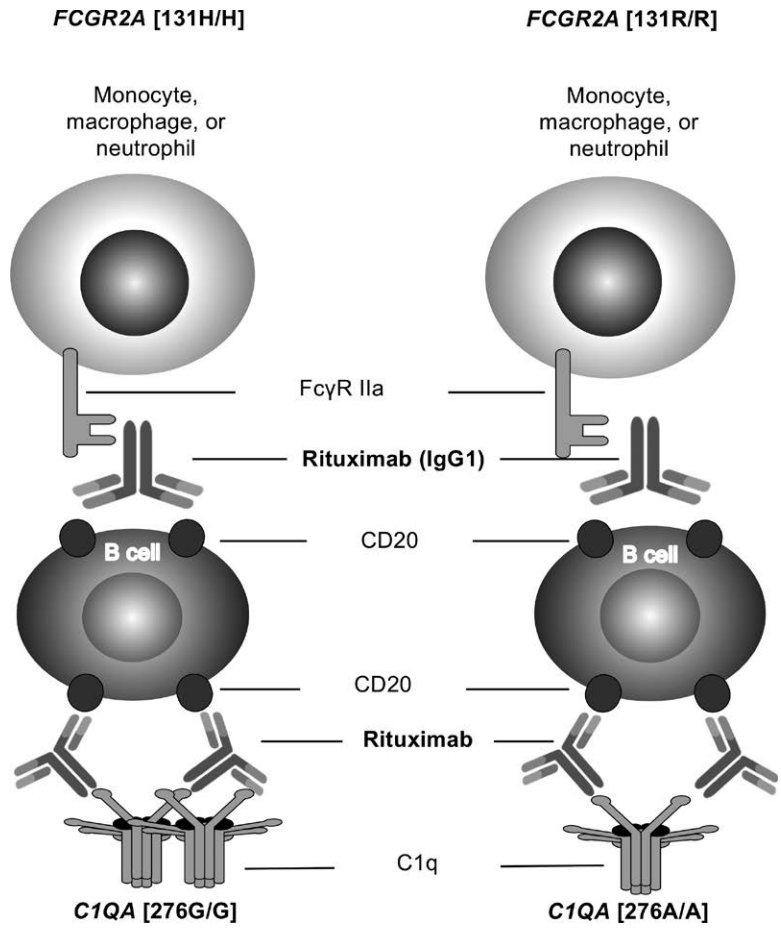

FIGURE 7. Schematic representation of the mechanisms of action of rituximab on B cells and the associated immunogenetic gene polymorphisms. In complement-dependent cytotoxicity, the binding of rituximab to serum complement components—particularly C1q—initiates a cascade of complement-related reactions that results in a membrane-invasion complex and subsequent B-cell death (bottom). In antibody-dependent cytotoxicity, rituximab mobilizes various combinations of natural killer (NK) cells, monocytes, macrophages, and neutrophils by binding to their Fcγ receptors, leading to the release of granzymes and other substances and, ultimately, B-cell death.

may explain the slower rituximab-induced B-cell depletion in LT recipients than in KT recipients.[50]

Role of Single-nucleotide Polymorphisms in B-cell Depletion by Rituximab

Antibody-dependent cellular cytotoxicity is initiated by interactions between the Fc segment of IgG and Fcγ receptors on monocytes, macrophages, dendritic cells, and natural killer (NK) cells, leading to the killing of antibody-coated target cells that express neoplasm- or pathogen-derived antigens on their surfaces. Numerous associations between antibody-dependent cellular cytotoxicity, Fc receptor single-nucleotide polymorphisms, and clinical outcomes have been observed in therapy with monoclonal antibodies. A single-nucleotide change in the gene encoding FCGR2A [131H/R] (rs1801274) places either histidine (H) or arginine (R) at position 131[10]; IgG1 binds more strongly to cells that have FcγRIIa [131H/H].[51] In B-cell non-Hodgkin lymphoma, these mutations in FCGR2A and FCGR3A are reportedly associated with clinical outcomes associated with rituximab administration.[52]

In the setting of ABO-I LDLT, the effects of rituximab on B cells were more profound in recipients with FCGR2A [131H/H] than in those with FCGR2A [131H/R or R/R]; these results were associated with stronger depletion of immunoglobulin in the sera of patients treated with rituximab, leading to an increased incidence of infectious complications in FCGR2A [131H/H] recipients.[53] Therefore, specific single-nucleotide polymorphisms of genes encoding Fcγ receptors may be predisposing factors for the intrinsic or adverse effects of rituximab in ABO-I LT.

Influence of Rituximab on T-cell Responses

Treatment with rituximab may affect the response of T cells to allogeneic antigens, given that B cells are effective antigen-presenting cells that can activate donor-specific T cells in secondary and intragraft tertiary lymphoid organs. In this regard, a variety of observations have been reported, but no definitive theory has yet arisen from them. A randomized double-blind placebo-controlled study revealed that B-cell depletion due to rituximab did not affect T-cell function in KT recipients.[54] In contrast, rituximab-induced cytokine release syndrome has been suggested to promote T-cell activation and increase the incidence of acute LT rejection.[55] Conversely, another study showed that rituximab can modulate immune responses by inducing the secretion of cytokines—particularly IL10 and macrophage inflammatory protein 1β.[56]

To determine the effect of rituximab on T cells, one group used MLR assays to compare the allogeneic immune responses of ABO-C and ABO-I KT/LT recipients and found a minimal effect of rituximab on alloreactive

T-cell responses after either KT or LT.[50] Of note, neither ABO-I KT nor LT recipients treated with desensitization therapy showed any change in allo-response in the mixed lymphocyte reaction after rituximab administration. However, both KT and LT recipients with pre-existing donor-specific antibodies demonstrated a significantly increased allo-response in the mixed lymphocyte reaction after rituximab administration.[57] These results suggest that treatment with rituximab undesirably depletes B-cell subsets that regulate sensitized T-cell responses to alloantigen. Further refinement of the desensitization protocol, as well as the development of novel agents, may be required to improve the outcomes in highly sensitized recipients.

Proposed Strategy for Selectively Inhibiting B-cell Responses to Blood-group Antigens

Although the use of rituximab greatly reduces morbidity in AMR, multiple or large rituximab doses significantly increase the incidence of infectious complications.[12] The development of therapies that selectively inhibit the responses of B cells to blood-group antigens, instead of the elimination of pan-B cells, would reduce the incidence of infections, resulting in further improvement of the outcomes of ABO-I LT.

Previously, invariant natural killer T cells were shown to play a critical role in the production of antibodies against the blood group A antigen in a mouse model.[55] These cells stimulate B cells to produce antibodies against ABO blood-group antigens via interactions between the invariant T-cell receptor, CD1d, and IL5 production (Figure 8). Anti-CD1d monoclonal antibody inhibits the production of antibodies against blood group A antigens, and its use may potentially reveal a novel therapeutic approach that prevents AMR without B-cell elimination in ABO-I transplant recipients.

Another insightful study has demonstrated the safety and feasibility of using mesenchymal stem cells to replace rituximab in ABO-I LT.[58] Transfusion of mesenchymal stem cells is comparable to rituximab treatment for AMR prophylaxis after ABO-I LT. In addition, the study results indicated that mesenchymal stem cells are more beneficial than rituximab in terms of preventing infection and biliary complications.[59] The use of mesenchymal stem cells could become a novel immunosuppressive approach to ABO-I LT.

Immunological Accommodation in ABO-incompatible Transplantation: Lessons From KT

When antibodies can be reduced to safe levels before ABO-I transplantation, even despite high antibody titers before desensitization, patients seldom develop AMR, and they maintain low antibody titers post transplantation. This phenomenon is known as "immunologic accommodation": although the vascular endothelial cells in the graft carry ABO antigens on their surfaces, and despite the presence of anti-A/B antibodies against those antigens in the blood of the recipient, no antigen-antibody reaction (ie, acute AMR) occurs.[60] Even in LT, donor-specific hyporesponsiveness remains after ABO-I LDLT, particularly in pediatric patients. The long-term persistence of blood antigens may contribute to donor-specific hyporesponsiveness.[61]

Two major hypotheses regarding the induction and maintenance of immunological accommodation have been proposed; they focus on factors associated with the donor compared with the recipient. Suggested important donor factors include attenuation or alteration of the antigenicity of blood-type carbohydrate antigens expressed on graft endothelial cells; the disparate expression of AB antigens on kidney endothelial cells and red blood cells; and the control of complement activation. Downregulation of

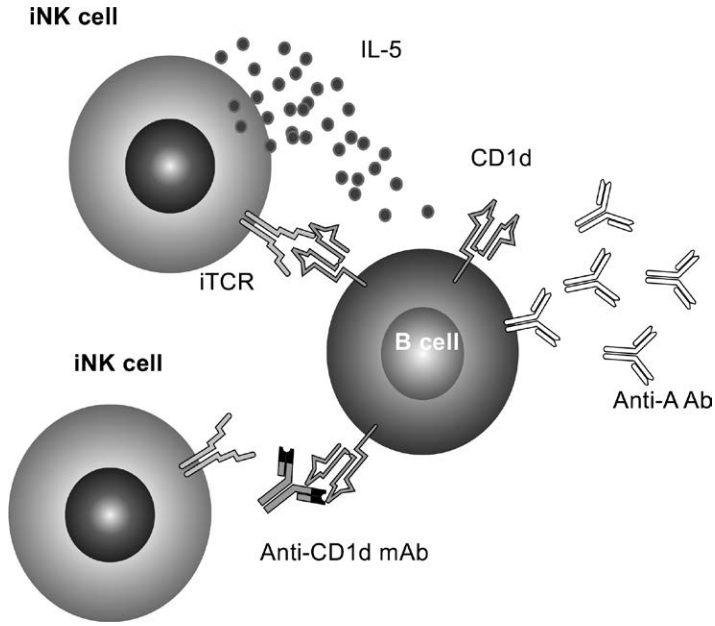

FIGURE 8. Production of antibodies to ABO blood-group antigens via interactions among the invariant T-cell receptor, CD1d, and IL5 production. Invariant natural killer (iNK) cells stimulate B cells to produce antibodies against ABO blood-group antigens through interaction among the invariant T-cell receptor (iTCR), CD1d, and IL5 production. Conversely, monoclonal anti-CD1d antibody (anti-CD1d mAb) blocks the production of antibodies to A antigens (anti-A Ab), thus potentially revealing a novel therapeutic strategy for preventing AMR in ABO-I transplant recipients. IL, interleukin.

donor-specific anti-A/B antibody production has been suggested as a recipient factor.

Attenuation or Alteration of Antigenicity

Continued expression of donor blood-group antigens on graft endothelial cells after ABO-I KT has been reported.[62] In contrast, one study reported a decrease over time after transplantation in the number of ABO-antigen–positive vessels compared with that of $CD34^+$ vessels (≤10 y, 66.5%; >10 y, 47.7%), and 10-y renal biopsies were negative for C4d staining in the peritubular capillaries. However, donor antigens never completely disappear.[63]

Disparate Expression

Another important point is the disparate expression of AB antigens on kidney endothelial cells and red blood cells. ABO antigens are carbohydrate antigens, the core structures of which are described as types 1 through 4. Whereas red blood cells carry all 6 structure types, kidney endothelial cells have mainly type 2.[64]

Control of Complement Activation

In human EA.hy926 endothelial cells transfected with the gene for blood type A- or B-transferase, preincubation with an anti-A/B antibody inactivated the ERK1/2 pathway and increased the abundance of complement regulatory proteins, such as CD55 and CD59.[65]

Downregulation of Donor-specific Anti-AB Antibody Production

Recipient-associated factors may play a key role in the induction and maintenance of immunological accommodation. In one group of ABO-I KT recipients, 84% had persistently low antibody titers (≤1:4) against donor blood-group antigens.[66] To exclude the effects of absorption of the antibodies by the grafts in vivo, the investigators cultured the recipients' peripheral blood mononuclear cells in vitro and measured the antibody levels in culture supernatants. In 60% of recipients, antibody titers (IgG and IgM) against donor blood group antigens remained ≤1:4. However, the cultured mononuclear cells of these accommodated recipients also produced antibodies against nondonor blood-group antigens and the carbohydrate epitope Gal.[66]

FUTURE CHALLENGES

Strategies to Treat AMR

Preemptive and Early Treatment

So far, early diagnosis of AMR through liver biopsy, followed by treatment involving a steroid pulse, PE, and IVIG, is practical.[19] Experience suggests that the first signs of AMR are fever and increased C-reactive protein levels. When these are observed concomitant with elevated liver chemistries on days 5 to 10 after transplantation, hepatic biopsy followed by a 1-shot steroid pulse is recommended. The isoagglutinin titer may not increase in patients who have received preoperative rituximab treatment, but liver function may begin to deteriorate in this setting. When liver biopsies reveal portal edema and necrosis (PEN), a complete steroid pulse regimen and IVIG are recommended.[19] Once transaminases increase rapidly, enhanced computed tomography is recommended to detect liver necrosis. In addition, ultrasonography is sensitive to intrahepatic biliary complications and reveals scattered stenosis and dilatation of intrahepatic bile ducts.

Next-generation Treatments

Once the process of AMR is initiated, rituximab is ineffective.[6,7] Plasma cell-depleting agents, such as the proteasome inhibitor bortezomib, are approved by the US Food and Drug Administration for the treatment of plasma cell dyscrasia and may be used in ABO-I LT recipients with caution. Bortezomib selectively induces apoptosis in plasma cells, decreasing antibody production.[67] One recent case highlights the significant potential of bortezomib against refractory, acute-phase AMR after ABO-I LDLT: numbers of early plasma ($CD19^+/CD20^-$) cells remained increased after rituximab administration but were depleted after bortezomib treatment (Figure 9).[68]

In addition to decreasing the amount of antibody, a treatment for decreasing or eliminating post transplantation inflammation might ameliorate the epithelial injury that leads to fatal AMR. For example, C1 and C5 inhibitors have been used successfully in the field of HLA-related donor-specific antibody.[69,70] IL6 is a critical growth factor for B cells and plasma cells and is produced in copious amounts by plasmablasts. Inhibiting IL6 significantly reduces the numbers of T_{fh} cells and plasmablasts and thus upregulates Treg cells. In addition, anti-IL6R/IL6 therapy reduces IL6 production in activated endothelial cells, subsequently reducing intimal proliferation and obliterative vasculopathy.[71]

The IgG-degrading enzyme of *Streptococcus pyogenes* (IdeS) is a bacterial endopeptidase that has the unique property of rapidly cleaving human IgG at the hinge region into Fc and F(ab′)2 fragments. IdeS cleaves human IgG and permits successful kidney transplantation using high-strength donor-specific antibody.[72]

Avoidance of Infectious Complications

In a Korean single-center study, the incidences of bacterial pneumonia, fungal pneumonia, and CMV infection of patients treated with preoperative rituximab before ABO-I LDLT were similar to those of patients undergoing ABO-C LDLT.[13] A Japanese multicenter study reported a significantly decreased incidence of fungal infection in patients treated with rituximab; the authors commented that rituximab prophylaxis decreased AMR such that the overall steroid dose could be reduced.[12]

Conversely, increased doses and multiple administrations of rituximab increase the incidences of fungal infection and CMV infection (Table 2). In an attempt to balance between the risks of infection and AMR, a single administration of rituximab at a dose of 375 mg/m^2 or of 500 mg in total has become standard. A study of single-nucleotide polymorphisms suggested that FCGR2A [131H/H] could indicate a high risk of infectious complications secondary to strong depletion of immunoglobulin.[53]

Streptococcal infection is speculated to lead to the reactivation of B cells, ultimately triggering AMR. Preventing infection might be important to avoid both B-cell reactivation and death.[73]

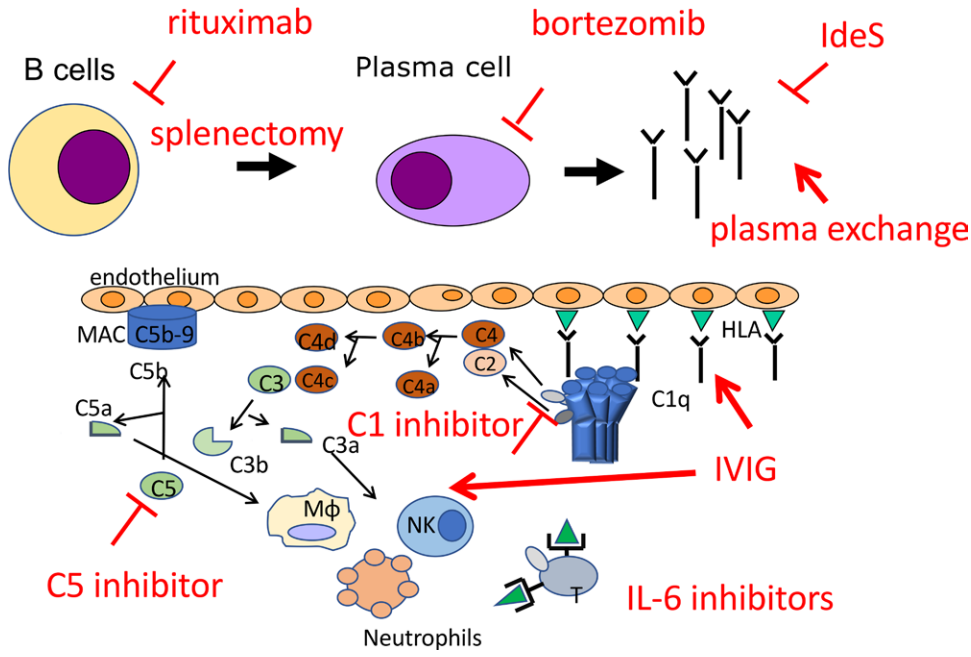

FIGURE 9. Mechanisms of current and future anti-AMR treatment strategies. Rituximab depletes B cells; bortezomib depletes plasma cells; the IgG-degrading enzyme of *Streptococcus pyogenes* (IdeS) cleaves human IgGs; C1 and C5 inhibitors ameliorate the complement cascade; and anti–IL6R/IL6 therapies reduce IL6 production. IgG, immunoglobulin G; IL, interleukin; MAC, membrane attack complex; Mø, macrophage; NK, natural killer cell; IVIG, intravenous immunoglobulin.

TABLE 2.

Impacts of combination of rituximab dose level and number on infectious complications

	Lx1 (n = 60)	Lx2 (n = 6)	Rx1 (n = 134)	Rx2 (n = 16)	Rx3 (n = 16)	*P*
AMR	12%	16%	6%	0%	0%	NS
Bacterial infection	38%	33%	26%	19%	42%	NS
Fungal infection	0%	0%	4%	6%	25%	<0.05
Viral infection	35%	0%	41%	94%	100%	<0.0001

AMR, antibody-mediated rejection; L, low dose (300 mg or less per administration); Lx1, 1 administration at low dose level; Lx2, 2 administrations at low dose; NS, not significant; R, regular dose (375 mg/m^2 or 500 mg total per administration); Rx1, 1 administration at regular dose; Rx2, 2 administrations at regular dose; Rx3, 3 administrations at regular dose.

TABLE 3.

Patient survival among age groups in 1099 patients after ABO-incompatible living donor liver transplants in Japan from 1989 to 2017

	1 y (%)	3 y (%)	5 y (%)	10 y (%)	15 y (%)	20 y (%)	25 y (%)
0–2 y	88.6%	86.9%	86.5%	85.1%	84.2%	81.8%	81.8%
3–17 y	77.2%	74.7%	72.7%	67.8%	59.8%	59.8%	59.8%
18 y and older	75.5%	69.5%	66.7%	60.3%	56.8%	56.8%	56.8%

Patient survival in the 0–2 y age group was significantly longer ($P < 0.0001$) than for the other groups.

TABLE 4.

Comparison of patient survival among ABO blood-type compatibilities in 1459 patients after living donor liver transplants in Japan from 2013 to 2017

	1 y	3 y	5 y
ABO-matched patients (n = 728)	89.0%	86.9%	82.7%
ABO-compatible patients (n = 282)	88.1%	86.9%	84.1%
ABO-incompatible patients (n = 217)	84.3%	79.1%	74.0%

Patient survival did not differ among the three groups ($P = 0.0851$).

Long-term Outcomes

The Japanese registry published in 2019 includes 8572 patients who underwent LT from 1989 to 2017; it reported patient survival of as long as 25 y.[74]

Patient survival after ABO-I LDLT plateaued after 10 y (Table 3). The 5-y survival rate of adult patients in the total cohort was 66.7%; among patients after 2013, when rituximab prophylaxis became standard for adult ABO-I LDLT, 5-y survival increased to 74.0% (Tables 3 and 4).[74] In single-center studies of ABO-I for HCC in Korea, 5-y survival rates varied from 74% to 86%.[38-40]

To improve the long-term outcomes of ABO-I LT, steady efforts to overcome the morbidity related to immunosuppressive drugs, recurrence of original diseases, de novo malignancy, and rejection are required. Paired exchange is another option to avoid ABO-I LT.[75-77] Donors were related and directed in 1 paired interchange case in Hong Kong and in 11 of 13 paired exchange cases, whereas 7 of 10 living paired exchanges in the United States were initiated by nondirected O donors.[75-77] The last reported case of a paired exchange for LDLT in Korea was in 2011, but paired exchanges are being developed in the form of LDLT chains in the United States.[75,77]

In practice, balancing the risks and timing of surgeries between paired matches can be very difficult. In addition, although we preoperatively matched 2 pairs of donor exchange patients in terms of risks and timing, their outcomes were quite different because of the many factors that influence the outcomes of LDLT recipients.[75] Any donor interchange for LDLT should occur in the context of a small-scale clinical trial with rigorous monitoring to ensure the safety and physical and psychological well-being of the donors.[76]

CONCLUSIONS

A desensitization protocol consisting of rituximab (375 mg/m^2), tacrolimus, and MMF before LDLT and followed by standard immunosuppression is currently the best in terms of cost, safety, and efficacy. Strategies to distinguish patients at a high risk of AMR and to adjust immunosuppression to prevent both AMR and infection are needed. Specific single-nucleotide polymorphisms in genes encoding Fcγ receptors may contribute to rituximab's effects on B-cell depletion. Immunological accommodation after ABO-I LT may be a topic for future study.

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