

Current techniques for ABO-incompatible living donor liver transplantation

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Abstract

For a long time, it was considered medical malpractice to neglect the blood group system during transplantation. Because there are far more patients waiting for organs than organs available, a variety of attempts have been made to transplant ABO-incompatible (ABOi) grafts. Improvements in ABOi graft survival rates have been achieved with immunosuppression regimens and plasma treatment procedures. Nevertheless, some grafts are rejected early after ABOi living donor liver transplantation (LDLT) due to antibody mediated rejection or later biliary complications that affect the quality of life. Therefore, the ABOi LDLT is an option only for emergency situations, and it requires careful planning. This review compares the treatment possibilities and their effect on the patients' graft outcome from 2010 to the present. We compared 11 transplant center regimens and their outcomes. The best improvement, next to plasma treatment procedures, has been reached with the prophylactic use of rituximab more than one week before ABOi LDLT. Unfortunately, no standardized treatment protocols are available. Each center treats its patients with its own scheme. Nevertheless, the transplant results are homogeneous. Due to refined treatment strategies, ABOi LDLT is a feasible option today and almost free of severe complications.

Key words: Living-donor liver transplantation; ABO-incompatible; Rituximab; Desensitization; Iso-titer; Biliary complications

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Core tip: Due to refined treatment strategies, ABO-incompatible living donor liver transplantation (ABOi LDLT) is a feasible option today and almost free from severe complications, but biliary complications still affect the quality of life after ABOi LDLT. Until now, the best improvement could be reached with the prophylactic

use of rituximab more than one week before AB0i LDLT.

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INTRODUCTION

Blood group antigens are expressed in almost every cell in the body, and an individual develops antibodies against blood group antigens (anti-A/B antibodies) absent in his or her own tissue. Grafts expressing foreign A/B antigens are usually hyperacutely rejected^[1]. For a long time, it was considered medical malpractice to neglect the blood group system during cadaveric transplantation. Because there are far more patients waiting for organs than organs available, a variety of attempts have been made to transplant AB0-incompatible (AB0i) grafts. Most AB0i liver transplantations (AB0i LTs) have had a lower graft survival rate due to hepatic arterial thrombosis, various biliary complications or acute rejection episodes^[2-4]. In those rejection episodes, the graft was damaged by necrosis or disseminated intravascular coagulopathy^[4,5]. This susceptibility to rejection can be explained sufficiently by blood group antigens that are expressed on the vascular endothelium and in large bile ducts for up to 150 d after transplantation^[6-10].

Young children with an incompletely developed immune system seem to be an exception. In 1979, Starzl's group reported eleven human AB0i LTs without evidence of acute rejection after transplantation^[11].

Because AB0i LTs need a certain amount of prearrangement, we focus in this review on AB0i living donor liver transplantation (LDLT), which is conducted electively, and neglect cadaveric AB0i LT.

In Western Europe and the United States, few case reports of AB0i LDLT exist, even though new techniques are available to overcome the blood group barrier^[6,12-17]. In Asia, Japan and South Korea, elective AB0i LDLT is performed with excellent results. Due to religious beliefs, fewer organs of deceased individuals are donated, and AB0i LDLT has become well established^[18,19]. Patients demonstrate survival with an AB0i graft for nearly as long as patients with an AB0-compatible (AB0c) graft^[18-21]. Improvements in AB0i graft survival rates have been achieved with immunosuppression and plasma treatment procedures (PTPs). The antibody titer (iso-titer) level cannot explain all clinical findings. However, hyperacute or acute antibody-mediated rejection (AMR) is closely related to hepatic necrosis or intrahepatic biliary complications^[22]. Additionally, patients with a history of immunizations are at higher risk for AMR. Blood group incompatibility, recipient age, etiology of liver disease and transplant era were found

to be significant predictors of overall survival, too^[23].

Various treatment protocols have been used for iso-titer elimination in AB0i LDLT patients. They originate from AB0i kidney transplantation protocols and do not follow a common standard. The iso-titer itself has also not been standardized. The results as well as its interpretation depend on the examining laboratory. Therefore, this review compares several treatment possibilities and their effect on graft outcome from 2010 to the present.

INDICATIONS FOR AB0i LDLT WITH SPECIAL REFLEXIONS

Pediatrics

The younger the child, the fewer iso-titers have been developed. In the first month of life, children are able to tolerate an AB0i graft very well. Preformed antibodies are absent, and the immune system is highly tolerant^[24].

Gurevich *et al.*^[25] examined 58 pediatric patients undergoing AB0i LDLT with a preoperative iso-titer of < 1:16. No graft rejection or death occurred and 93% survived beyond the first 10 years. Patients with biliary atresia had fewer rejection episodes in situations where the graft was donated by the mother (mother:father vs 40%:55%)^[25-27]. Most data in children have been collected in Asia^[25,28]. Okada *et al.*^[29] described rituximab to be successful in pediatric AB0i LDLT. Kasahara *et al.*^[23] analyzed 2224 pediatric transplantations, the largest cohort worldwide. They found 1-, 5-, 10- and 20-year patient survival rates of 88.3%, 85.4%, 82.8% and 79.6% in the 294 patients undergoing AB0i LDLT.

Acute liver failure

In Europe and the United States, emergency AB0i LDLT is conducted only if no compatible donor can be acquired in time^[8,30]. In Asia, this concept is more common. Shen *et al.*^[31] for example, reported 3-year patient survival rates in AB0c vs AB0i LDLT of 83.1% vs 86%. The graft survival was 80% vs 86%. Two AB0i patients developed AMR, but no other patients had cellular rejection, biliary complications or infections. A model of end stage liver diseases (MELD) score > 30 put patients at high risk for mortality. For this reason, in the Asian Medical Center, the largest LDLT center in the world, Lee *et al.*^[18] excluded high-urgency patients from AB0i LDLT. Shinoda *et al.*^[32] in contrast, found no difference between AB0c and AB0i LDLT.

Hepatocellular carcinoma

Living donation provides an alternative curative treatment option for patients with hepatocellular carcinoma (HCC) in cirrhosis if no offers for deceased donor organs exist. This can be due to low laboratory MELD scores or if the tumor burden is beyond the Milan criteria. There are only a few reports of successful AB0i LDLT in patients with HCC outside Milan^[33]. After Lee *et*

Table 1 Research regarding ABO-incompatible living donor liver transplantation published since 2010

Ref.	Pat No.	Splenectomy local graft infusion	Rituximab	IVIG	PTP Target iso-titer	IS	AMR
Lee <i>et al</i> ^[59]	15	-/-	-14 d 300 mg/m ²	+1, +4 d 0.8 g/kg bw	First -7 d 1:8	Triple	No
Shen <i>et al</i> ^[31]	35	n.s.	Z 375 mg/m ²	Z 0.4 g/kg bw	Rescue	Quadruple	2
Lee <i>et al</i> ^[59]	15	-/-	-14 d, 300 mg/m ² Z, +4 d, 200 mg/m ²	No	TPE < 1:8	Triple	No
Kim <i>et al</i> ^[36]	14	-/-	-7 d 375 mg/m ²	+1, +3, +5 d 0.6 g/kg bw	TPE 1:32	-3 d MMF 1.5 g triple	No
Song <i>et al</i> ^[52]	10	-/+	-14 d, 375 mg/m ²	No	TPE 1:32	Triple with Cyc	No
Kim <i>et al</i> ^[20]	22	-/-	-14 d, 375 mg/m ²	No	PP 1:32	PGE1 Triple	No
Lee <i>et al</i> ^[34]	20	-/-	-15 d 300 mg/m ²	+1, +4 d 0.8 g/kg bw	TPE < 1.16	Quadruple	No
Song <i>et al</i> ^[66]	20	-/+	-21, -14 d 300, 375 mg/m ²	No	TPE 1:8	Triple with Cyc	No
Song <i>et al</i> ^[66]	21-127	-/-	-21, -14 d 300, 375 mg/m ²	No	TPE 1:8	Triple	No
Song <i>et al</i> ^[66]	128-235	+/-	-21, -14 d 300, 375 mg/m ²	No	TPE 1:8	Triple	17
Yasuda <i>et al</i> ^[67]	5	+/-	-15, -3 d 500 mg/m ²	No	TPE n.s.	Triple	4
Lee <i>et al</i> ^[35]	19	-/-	-10 d 300-375 mg/m ²	No	TPE 1:32	-7 d Tac 0.1 mg/kg, quadruple	No
Lee <i>et al</i> ^[68] (Initial iso-titer < 1:64)	20	-/-	+1 d, 375 mg/m ²	No	< 1:64	Quadruple	No
Lee <i>et al</i> ^[68] (Initial iso-titer > 1:64)	26	-/-	-21 d, 375 mg/m ² +1 d, 187 mg/m ²	No	TPE/PP < 1:64	Quadruple	No

Quadruple: Tacrolimus, mycophenolate mofetil, basiliximab, steroids; Triple: Tacrolimus, mycophenolate mofetil, steroids; TPE: Therapeutic plasma exchange; IS: Immunosuppression: 5 d before transplantation - 5 d, 5 d after TX - +5 d, day of TX - Z; Cyc: Cyclophosphamide; PP: Plasmapheresis, not otherwise specified; PGE1: Prostaglandin E1, gabexate mesilate; Tac: Tacrolimus.

a^[34] experienced a recurrence of 57% in the first year after ABOi LDLT, they recommended refraining from transplanting HCC patients^[34].

Peter and Werny investigated a distinctly higher anti-A/B titer in patients with severe emaciating diseases compared to healthy blood donors^[30]. HCC patients seem to have very high anti-A/B titers and a strong rebound. This increase could relate from altered expression of blood group antigens on the biliary tree in pathological conditions^[23]. Neoeexpression or aberrant expression of A or B substances in malignant cells possibly boost the production of antibodies^[24]. In this situation, the tumor bulk might define the antibody titer and rebound.

Hepatitis B/C

Lee *et al*^[34] described ABOi LDLT in 20 patients. The etiology of liver diseases consisted mostly of HBV infections ($n = 15$) and one hepatitis C virus (HCV) infection. To prevent hepatitis C virus (HBV) recurrence, Lee *et al*^[34] used entecavir or tenofovir with a high dose of intravenous (IV) HB-hyperimmune globulin. If HCV was confirmed by a liver biopsy or an abnormal liver function test with elevated HCV RNA loads, PEGylated-interferon and ribavirin were administered. Other authors describe ABOi LDLT in patients with HBV or HCV cirrhosis and in patients with HCC, as well. Unfortunately, they provide

no information about their hepatitis therapy or antibiosis (Table 1)^[20,35,36]. No data are available on ABOi LDLT in HCV patients with the new antivirals.

TREATMENT STRATEGIES TO OVERCOME BLOOD GROUP BARRIER

ABOi LDLT requires careful planning and logistical preparation prior to surgery. As treatment regimens vary distinctly, we would like to present them in the following way. All regimens have the focus on antibody reduction in common. To reach this goal and to prevent antibody rebound as well, therapeutic apheresis is combined with immunosuppressive therapy. A good overview is given in a South Korean treatment schedule: Prior to transplantation rituximab and plasma exchange is started. When the anti-A/B titer has decreased to at least a titer of 1:8, transplantation takes place without local infusion or splenectomy. Afterward, immunoglobulins and quadruple immunosuppression are administered.

Anti-A/B iso-titer

As Warner *et al*^[37] summarized, "The durable survival of ABOi solid organ allografts seems to be primarily dependent on 3 conditions: (1) the low expression of antigen on the graft, as in case of A2 positive organs; (2)

a low titer of anti-donor ABO antibodies in the recipient before transplantation; and (3) the ability to maintain low titers of antidonor ABO antibodies in the recipients after transplantation, at least for the first 3 to 6 week^[37]. In the setting of ABOi LDLT, iso-titers naturally rise during the first two days after transplantation^[38]. In addition to the natural rebound, de novo alloantibodies have the potential to develop. This alloimmune reaction induces a higher rebound and can lead to AMR, putting the graft at risk. This makes the first two weeks, or even four to six weeks, after ABOi LDLT critical for AMR^[39].

After this period, the graft has been mostly adapted to its new environment. This state is called accommodation.

Furthermore, the target titer for IgG and IgM in ABOi LDLT varies from center to center. Some centers estimate 1:8 to be appropriate, others 1:16^[39]. However, a titer of 1:64 or above should be avoided due to an increased risk of complications during transplantation and AMR^[30,40]. In the studies we compared in Table 1, titers of 1:64 or above were not accepted and lead to further PTPs (Table 1).

Therapeutic apheresis

Therapeutic apheresis is the most effective way to control the humoral antibody response to prevent rejection^[41]. There are a variety of PTPs, which differ mainly in their selectivity toward immunoglobulin elimination.

Therapeutic plasma exchange: Therapeutic plasma exchange (TPE) is a widely accepted nonselective PTP to eliminate antibodies in patients with solid-organ transplants which are sensitive to HLA antigens or undergo ABOi transplantation. Still, no controlled studies of TPE in ABOi LDLT or therapy standards have been published. With TPE, usually 1.2 times (1.0-1.5) the patient's plasma volume is treated. The amount of treated plasma volume correlates with the removal of 63% to 72% of the original plasma constituents. At the end of a TPE procedure, IgM is very low. High levels of IgM are usually reduced with one or two TPE^[42]. The American Society of Apheresis guidelines designate the perioperative use of TPE in ABOi LDLT as a category I with 1C recommendation^[43]. Moreover, the use of double-volume TPE pre-transplant eliminated more than 90% of the antibodies, lead to an iso-titer of < 1:16 and decreased the episodes of rejection^[44]. In the studies we reviewed, PTP was conducted before and after ABOi LDLT. Almost all centers used TPE to eliminate anti-A/B iso-titers (Table 1).

Immunoadsorption: Immunoadsorption (IA) is mainly performed in Western Europe. Controlled studies of IA are still lacking in the setting of ABOi LDLT. With IA, it is possible to deplete a large amount of circulating antibodies without considerable loss of essential plasma constituents. Two IA-methods are available to selectively reduce antibodies. The first is the blood group

antigen-specific apheresis (Glycosorb® ABO, Glycorex Transplantation, Lund, Sweden). This technique is preferred to reduce the iso-titer. Because the IA-column is highly selective for anti-A/B antibodies, other antibodies are not affected and no replacement fluid is required. With each plasma volume treated with Glycosorb®, the iso-titer of IgG and IgM is reduced by one titer. Compared to the baseline, a reduction to 59% for IgG iso-titer and to 30% for IgM iso-titer is considered average^[45].

The second is the semiselective antibody removal (Immunosorba®, Globaffin®, Fresenius Medical Care, Bad Homburg, Germany, Therasorb®, Miltenyi Biotec GmbH, Bergisch Gladbach, Germany). These columns mainly bind IgG and, to a lesser degree, IgM, regardless of their specificity. This unspecific removal is beneficial for transplant candidates with an additional sensitization. In ABOi kidney transplant patients, a single session of IA decreased anti-A/B IgG iso-titers more effectively than antigen-specific apheresis. IgG was reduced to 28% of the baseline value and IgM to 74%^[45]. In the studies we compared, the use of IA was not reported, as IA is only common in Europe. Asian centers use TPE or double-filtration plasmapheresis instead (Table 1).

Double-filtration plasmapheresis: Outside of Japan, the use of double-filtration plasmapheresis for ABOi LDLT is very limited. The Evaflux™ 2A (Kawasumi laboratories, Japan) eliminates IgG as well as IgM. After processing 1000 mL plasma, the ratio of solute returned to the patient, or the sieving coefficient, is 0.00 for IgM and 0.19 for IgG. As the value of 0.00 for IgM indicates, these pore-based filter columns are most effective for IgM depletion. The target iso-titer < 1:16 was reached with only 4 treatments, even in cases with very high initial iso-titers (> 1:2048)^[46].

Intravenous immunoglobulin G

Intravenous immunoglobulin G (IVIG) are suggested to be beneficial in immunoregulation because they block Fc receptors on mononuclear phagocytes and directly neutralize alloantibodies. They also inhibit the expression not only of CD19 on activated B cells and the complement system but also of alloreactive T cells^[13]. In the field of transplantation, IVIG was used with PTPs in pre-sensitized recipients or to treat AMR^[47,48]. IVIG can be used as a rescue therapy, in the case of severe AMR, if there is not enough time (three days) for rituximab to exert an effect^[39]. When IVIG is part of the therapeutic protocol, graft survival is estimated to be greater than 87%^[47,49,50]. Hanto *et al.*^[44] compared ABOi recipients receiving TPE and IVIG with patients receiving only TPE during the post-transplant period. In this study, the patient group with IVIG did not develop AMR, but 27.3% of the patients in the other group did develop AMR post-transplant. Unfortunately, a transient increase of anti-A/B titers is observed after IVIG administration due to the passive transfer of anti-A/B. Thus, IVIG should not be administered prior to ABOi LDLT. All

centers that we have compared report using IVIG after ABOi LDLT (Table 1).

Immunosuppression

Immunosuppression consists of steroids, calcineurin inhibitors and antimetabolites. In our center, we use quadruple immunosuppression: Monoclonal antibodies, calcineurin inhibitors, antimetabolites and steroids.

In 1998, Tanabe *et al*^[51] described a new protocol in which they, in addition to perioperative TPE and splenectomy, supplemented systemic immunosuppression with portal vein infusion therapy (PVIT). Methylprednisolone, prostaglandin E1 and gabexate mesilate were used in the PVIT. If PVIT causes portal vein thrombosis, Kozaki *et al*^[41]'s hepatic arterial infusion therapy (HAIT) could be conducted. The two most feared complications after PVIT or HAIT were thrombosis and bleeding.

In 2013, local graft infusion, in the form of hepatic arterial infusion (HAI) or portal vein infusion (PVI), with PGE1 was only performed by Kim *et al*^[20] and Song *et al*^[52]. Since 2010, only Song *et al*^[52] have also administered cyclophosphamide as immunosuppression. The therapeutic regimen after LDLT includes antifungal, antimicrobial and cytomegalovirus prophylaxis. However, dosage, medication and duration of the medication have not yet been standardized.

MONOCLONAL ANTIBODIES

Rituximab is a monoclonal chimeric human-murine anti-CD20 antibody that depletes B cells. It acts by complement- and antibody-dependent cell-mediated cytotoxicity. The CD20 antigen is expressed on pre- and mature B cells, but not on long living plasma cells persisting in the bone marrow. Hence, rituximab does not directly affect antibody-producing plasma cells. A single dose of rituximab in ABOi LDLT suppresses B cells for more than six months after transplantation in the peripheral blood^[4,50]. However, because B cells in the lymph node are unaffected, they are activated by the ABOi graft, and the anti-A/B titers rise for the first four to six weeks after transplantation^[4,50,53]. But even if antibody production is possible at low levels, de novo production of antibodies is sufficiently delayed due to rituximab^[28]. Monteiro *et al*^[54] reported the first case of ABOi LTX using rituximab in 2003. Usuda *et al*^[55] reported the first case of rituximab prophylaxis in ABOi LDLT in 2005. Egawa *et al*^[4] reported in 2014 that rituximab prophylaxis significantly decreased the incidence of AMR, especially severe AMR leading to hepatic necrosis ($P < 0.001$)^[4]. However, other B cell desensitization therapies have shown no additional effects in the rituximab group. Multiple or large rituximab doses significantly increased the incidence of infection and early administration held no advantage^[4]. All the transplantation centers we compared treated their ABOi LDLT patients with rituximab, with most of them administering it before transplantation. Two weeks before surgery tends to be an opportune time

(Table 1). Regarding the safety of rituximab in ABOi LDLT, pharmacodynamic studies have to be conducted to determine the safest dose. Currently, therapeutic regimens are adopted from the kidney transplantation protocols.

Basiliximab is a chimeric mouse-human monoclonal antibody to CD25 of the interleukin (IL)-2 receptor, located on the surface of activated T lymphocytes. It inhibits T cell proliferation and prevents cell-mediated rejection in liver transplantation^[56,57]. It prevents T-helper cells from replicating, blocks the activation of B cells and restricts the production of antibodies, including anti-donor isoagglutinin antibody. Recently, the regimen that combines rituximab with basiliximab in ABOi LDLT has been questioned^[4].

Splenectomy

The spleen is a major antibody reservoir, containing large amounts of B cells and plasma cells. Splenectomy before ABOi LDLT to prevent antibody rebound is becoming more controversial. Most Asian centers use protocols with splenectomy in addition to other immunosuppressive measures^[18]. However, several reports have shown that splenectomy does not offer any immunological advantage in ABOi LDLT. For example, Raut *et al.* observed no statistically significant differences in anti-A/B IgM and anti-A/B IgG titers between "splenectomy" and "non-splenectomy" groups^[58]. Several reports have also shown that splenectomy may not offer any immunological advantage in ABOi LDLT. The clinical outcomes, including AMR, biliary complications, infections and survival, were also similar in the two groups^[52,59,60]. An exception to this general rule are patients with imminent "small for size" syndrome, who have better outcomes after splenectomy^[4,61]. Only two centers of the ones compared carried out splenectomy. In these centers, 21 of 23 patients had AMR occurrence (Table 1).

Complications after ABOi LDLT

Biliary complications, which are still a major issue in ABOi LDLT, are likely related to immunological mechanisms. Donor blood group antigens are expressed for up to 150 d on the bile duct's epithelium after transplantation^[59,62-64]. Song *et al*^[7] reported a higher incidence of biliary strictures, especially diffuse intrahepatic biliary strictures (DIHBS), in ABOi LDLT than in ABOc grafts. These strictures significantly affected the overall survival^[15]. In Lee *et al*^[18]'s study, 5.6% of the patients developed complications, such as DIHBS, 2.1-5.2 mo post-transplant. In 2005, Kozaki *et al*^[41] showed that high preoperative anti-IgM iso-titer led to bile duct complications. High preoperative anti-IgG iso-titer led to hepatic necrosis and high postoperative anti-IgM and anti-IgG iso-titers lead to hepatic necrosis as well. Once hepatic necrosis occurred, no patient survived.

Biliary complications developed in 54%-82% of the ABOi allograft recipients, compared to 6% in

ABO matched allografts. Hepatic artery thrombosis also occurred in 24% of ABOi allografts^[3,28]. In 2011, the meta-analysis of Wu *et al.*^[64] showed increased complications and AMR in ABOi LDLT, as well.

Another complication, such as the “small for size” syndrome in ABOi LDLT, can be avoided *via* a new dual split technique from Asia^[65]. Dual LDLT with ABOi and ABOc grafts is a feasible solution for simultaneously overcoming both the ABO blood group barrier and small-for-size graft.

CONCLUSION

Since 2010, no new techniques in ABOi LDLT have been reported in medical journals, but the treatment options have been refined. The outcomes of ABOi LDLT are still inferior to those of ABO-compatible and identical LDLTs, and anti-A/B antibodies reappear after the transplant. However, due to refined treatment strategies, ABOi LDLT is a feasible option today and is almost free from severe complications. We compared the regimens of 11 transplant centers, as well as their outcomes from 2010 to the present. The best improvement in outcomes next to PTPs has been observed with the prophylactic use of rituximab more than one week before ABOi LDLT. Although each center treats its patients with its own scheme, the transplant results are homogeneous. In our center, we have had positive experiences starting quadruple immunosuppression with basiliximab before transplantation. We also use TPE or IA and reduce the iso-titer at least down to 1:8 prior to transplantation. If the iso-titer rises again afterward, we mainly perform TPE.

A new approach for overcoming both the ABO blood group barrier and small-for-size grafts seems to be the dual split LDLT with ABOi and ABOc grafts that has been conducted in Asia.

Still, ABOi graft survival in adults is poorly understood. Neither is the emergence of de novo anti-A/B, nor their impact. Graft accommodation gives a possible explanation for ABOi graft survival in the presence of donor specific antibody titers.

In the long term, iso-titer rebound prevention might be necessary to lower the risk of iso-titer mediated rejection even further. However, no specific medication is available yet to meet this need.

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