ABO-Incompatible Living Donor Liver Transplantation in Focus of Antibody Rebound

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Keywords

Transplantation · ABO incompatibility · Liver · Antibody rebound

Summary

Background: Living donor liver transplantation (LDLT) is an option to expand the donor organ pool for patients with life-threatening diseases who cannot be supplied with a cadaver organ. Next to the donor risks, complications after ABO-incompatible LDLT (ABOi LDLT) in the recipient are subject to controversial discussion. Improvement in ABOi graft survival rates have been achieved with plasma treatment procedures (PTP) and immunosuppression but antibody-mediated rejection (AMR) and graft loss still occur. **Methods:** Since 2008, we have prepared 10 patients for ABOi LDLT. Seven of the 10 patients for transplantation had hepatocellular carcinoma (HCC). **Results:** All patients underwent PTP before and after ABOi LDLT as well as immunosuppression according to the treatment schedule. We did not use anti-CD20 monoclonal antibodies in the transplant setting. We transplanted 6 of 10 preconditioned patients. After 3 years, 5 of the 6 transplanted patients were still alive. **Conclusion:** Even if B-cell depletion with anti-CD 20 treatment in the setting of ABOi LDLT is commonly accepted, our center successfully administered only quadruple drug immunosuppression combined with PTP. Especially patients with HCC had a high titer increment also pre-transplantation and were at high risk for arterial thrombosis and graft loss.

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Introduction

Due to donor organ shortage in Germany, living donor liver transplantation (LDLT) is an option to expand the donor organ pool for patients who cannot be supplied with a cadaver organ in spite of a life-threatening disease in time. Besides the donor risks, complications after ABO-incompatible living donor liver transplantation (ABOi LDLT) in the recipient are controversially discussed: arterial thrombosis, cellular and antibody-mediated rejection, sepsis and graft failure due to biliary complications as well as sepsis and liver necrosis [1–3].

Although the liver seems to be more resistant to hyperacute rejection than the kidney or heart, hyperacute rejection may occur in pre-sensitized recipients and in recipients of ABO-incompatible (ABOi) allografts [4]. Blood group antigens are not only present on the surface of blood cells, on which they were originally described, but also on the surface of the endothelium of vessels and in large bile ducts [5]. Vascular endothelium and the biliary epithelium of hepatic allografts may continue to express donor blood group antigens up to 150 days after transplantation [6, 7]. Therefore the ABOi graft may be more susceptible to hepatic artery thrombosis and to immunological bile duct injury [2, 8].

Improvement in ABOi graft survival rates has been achieved with plasma treatment procedures (PTP) and immunosuppression regimes. Nevertheless, early antibody-mediated rejections (AMR) and graft loss occur. Here preformed anti-A/B antibodies of the recipient are involved. The amount of acceptable anti-A/B is not standardized for ABOi LDLT. As mentioned in the literature, patients with titers > 1:16 underwent PTP before transplantation [9, 10]. In many cases, unless methods to maintain low anti-A/B titers after transplantation are used, depletion is only transient, and antibody titers rise again the first days after transplantation (post-transplantation rebound) [11]. This leads to rejection in 90% of all cases [12].

Silke Rummeler and Astrid Bauschke contributed equally to this paper.

Unlike in Asia, where LDLT and ABOi LDLT are often the only therapeutic option because of religious beliefs, in Western Europe only a few small case series to ABOi LDLT exist [1, 13, 14]. In Asia, the concept of ABOi LDLT is continuously tracked [15].

Since 1995, LDLT has been performed in the Department of General Visceral and Vascular Surgery at the University Hospital of Jena. The first ABOi LDLT took place in 2008. Here, we present our experience with ABOi LDLT in the perioperative setting.

Material and Methods

Anti-A/B Testing

Blood group was determined with commercially available antisera according to standard immunohematologic techniques. Anti-A/B titers were specified by direct agglutination at 22 °C and by indirect anti-human globulin (AHG) tested at 37 °C using A1, A2 or B test red blood cells, neutral gel cards and anti-IgG gel cards containing rabbit AHG (DiaMed, Cressier, Switzerland). Titers were recorded as inverted value of the highest plasma dilution giving a weak agglutination reaction (+1).

Titers were converted into whole numbers (1:1 = 1, 1:2 = 2, 1:4 = 3, 1:8 = 4, 1:16 = 5, 1:32 = 6, 1:64 = 7, 1:128 = 8, 1:256 = 9, 1:512 = 10, 1:1,024 = 11, 1:2,048 = 12) to calculate the titer reduction rate (TRR), and titer increment (TI) according to Wilpert et al. [9]. TRR was calculated as follows:

$$\frac{(\text{titer before treatment} - \text{titer directly before transplantation})}{\text{total number of treatments}} \quad (1).$$

The TRR > 1 reflects the effectiveness of the treatments. Titer recovery between the end of PTP and the beginning of the next treatment is TI. TI > 2 describes a high rebound. Titers were measured immediately before and after PTP. We attempted to keep the titers (IgG and IgM) as low as possible at the time of transplantation and below 1:8 during the first 2 weeks post ABOi LDLT. We decided to exclude IgM values from this study, as their titer was in every sample below the IgG titer. After ABOi LDLT, anti-A/B has been measured in the first 2 weeks daily in the morning and afterwards weekly or in case of abnormal findings. As soon as anti-A/B increased, the option of PTP has been discussed for every patient individually with the transplantation team.

Removal of Antibodies by PTP and Treatment Protocols

A continuous blood cell separator (Cobe Spectra®, TerumoBCT, Lakewood, CO, USA) was used to separate the blood. For anticoagulation we used citrate (ACD-A), while controlling ionized calcium, or a mix of citrate and heparin or argatroban.

Selective Immunoadsorption

Selective immunoadsorption (IA), mainly performed in Western Europe, has not been verified with controlled studies in the setting of ABOi LDLT yet. There are no guidelines available.

During IA, at first, plasma is separated from whole blood and then processed in the immunoadsorbent columns (Glycosorb® ABO, Glycorex Transplantation, Lund, Sweden). On the columns, A or B blood group antigens are linked to a sepharose matrix specifically depleting anti-A/B. Other antibodies remain unaffected, as the Glycosorb-column is highly selective for anti-A/B antibodies. No replacement fluid is required. On average, we treated 2.2 times the plasma volume in each procedure.

Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) is a generally accepted nonselective PTP, which eliminates antibodies in patients with solid organ transplants. The American Society of Apheresis guidelines designates the perioperative use of TPE in ABOi LDLT as a category I with 1C recommendation [16]. No controlled studies of TPE in ABOi LDLT have been published yet

Table 1. Patients overview

	Patients, years (range)
Mean age, years (range)	53 (33–63)
	n
Treated patients	10
Female	5
Male	5
Cirrhosis	1
Cirrhosis with HCC	7
Cirrhosis with cholangiocarcinoma	1
Giant hemangioma	1

We performed TPE in urgent cases and in patients with low titers ($\leq 1:16$).

The replacement fluid consisted of a 1:1 mix of therapeutic plasma Octaplas® LG (Octapharma GmbH, Langenfeld, Germany), or fresh frozen pathogen-reduced apheresis plasma (Institute of Transfusion Medicine Jena, Germany) and 5% human albumin (Albunorm®; Octapharma GmbH). We exclusively used AB plasma. In each procedure, 1.3 plasma volumes were processed.

Immunosuppression

All patients received quadruple immunosuppression consisting of steroids, calcineurin inhibitors, antimetabolites, and monoclonal antibodies. We did not use intravenous immunoglobulin and anti-CD20. Steroids were scheduled 7 days before transplantation, with 30 mg/day and 500 mg intraoperatively. Afterwards we continued with 1 mg/day/kg body weight (BW) and reduced the dose by 5 mg every 2 days until 7.5 mg was reached. Tacrolimus (Prograf®; Astellas Pharma, Tokyo, Japan) was started as pre-emptive immunosuppression 3 days before transplantation at 4 mg twice a day to achieve a plasma level of 10 µg/l. Mucophenolate mofetil (Cellcept®; Roche Pharmaceuticals, Basel, Switzerland) was also started 3 days before transplantation, 1 g every 12 h. On the 2nd and on the 4th postoperative day the interleukin-2 receptor antagonist Basiliximab (Simulect®; Novartis Pharmaceuticals, East Hanover, NJ, USA) was administered by i.v. infusion at 20 mg. For 10 days after transplantation, Iloprost (Ilomedin®; Bayer Vital GmbH, Leverkusen, Germany) was given at 1 ng/kg BW.

Patients

Since 2008 until 2013, we have prepared 10 patients with different indications for ABOi LDLT (table 1). The highest initial titer was 1:2,048 (anti-A) and the most often diagnosis HCC.

Written, informed consent for ABOi LDLT and PTP was obtained from each patient.

The positive vote of the local ethics commission was obtained with the number 4337–02/15.

Results

All patients underwent PTP before ABOi LDLT. On average, we performed 4 PTP (range 1–7) prior to ABOi LDLT, to overcome pre-transplantation rebound, and 6 PTP (0–12) after ABOi LDLT to overcome post-transplantation rebound (table 2). We completed all PTP as scheduled. Except mild citrate reaction, no side events or technical problems occurred. Especially after 3 PTP we observed an increased titer rebound, mainly in carcinoma patients.

Patients 1, 3, and 7 presented no clinical side effects before and after transplantation. By contrast, patients 5, 9, and 10 could not receive ABOi LDLT due to their risk profile and high pre-trans-

Table 2. Blood group combination, diagnosis for ABOi LDLT, TRR (>1 is efficient), mean TI (>2 is high) according to PTP and graft functionality

Patient	Blood group donor→recipient	Diagnosis	Anti-A/B initial	PTP pre LDLT	TRR	TI	Anti-A/B at LDLT	LDLTX performed	PTP post LDLT	Survival/graft function 2015
1	A1→O	cirrhosis	1:2048	5	1.0	0.59	1:32	yes	3	yes; >5 years
2	A1B→B	HCC	1:16	2	2.5	2.0	negative	yes	12	yes; >3 years
3	A1B→A1	giant hemangioma	1:8	1	2.0	1.5	1:2	yes	0	yes; >3 years
4	A1B→A1	HCC	1:128	3	1.33	2.44	1:1	yes	7	no; hepatic necrosis
5	A1→O	cholangiocarcinoma	1:2048	4	1.5	2.66	1:32*	no		
6	B→A1	HCC	1:512	4	0.66	2.0	1:128*	no		
7	A1B→A1	HCC	1:8	2	3.0	1.0	negative	yes	1	yes; >3 years
8	A2→B	HCC	1:32	5	0.8	1.77	1:2	yes	11	no; extrahepatic metastasis
9	A1→O	HCC	1:512	5	0.5	3.0	1:32*	no		
10	A1→O	HCC	1:512	7	0.5	2.5	1:16*	no		

*Preparation to LDLT has been stopped due to rebound.

plantation titer rebound. For 1 patient (no. 6) the donor organ was no longer available. The other 3 patients (no. 2, 4 and 8) rebounded strongly after surgery and were subsequently treated with PTP more often (fig. 1–3). These patients were transplanted despite TI ≥ 2 or TI > TRR and developed severe complications. One of these patients (no. 4) died due to hepatic failure within 1 week after transplantation and another (patient 8) developed a partial portal vein thrombosis, which resolved in the course of PTP spontaneously.

Five of our 6 transplanted patients developed biliary tract complications within 14 days after ABOi LDLT. All patients were only treated endoscopically.

After 3 years, 5 of the 6 transplanted patients were still alive.

With the use of Glycosorb, we were able to remove 2.1 titer steps by treating the 2.2-fold plasma volume. TPE shows the same results, even with the treatment of 1.3-fold plasma volume.

Discussion

We report here our experience with ABOi LDLT in a setting with PTP, using a conventional immunosuppressive protocol without administration of anti-CD20 monoclonal antibodies. In Western Europe only small case series for ABOi LDLT exist [14, 17–19].

In our study 5 of 6 transplanted patients are still in hold of their first transplanted organ 3 years after ABOi LDLT. Yet our study's results are clearly limited by the small number of patients we prepared for ABOi LDLT. Still, all patients with HCC presented a high anti-A/B titer and a strong pre-transplantation rebound prior to ABOi LDLT.

ABOi LDLT has always been a controversial issue. The focus of the debate includes severe cell-mediated rejection, AMR, vascular thrombosis, acute liver necrosis, bile duct complications, and sepsis.

Currently elective ABOi LDLT is performed in Asia with excellent results. There, ABOi LDLT patient survival is close to survival

rates of ABO compatible (ABOc) LDLT [20–23]. Due to less deceased organ donors, ABOi LDLT on an elective basis with living donor grafts has been well established, particularly in Japan and South Korea [22, 23].

One strategy in ABOi LDLT is to reduce antibody titers with PTP like TPE or IA. Using IA, 50–60% or 1–2 titer steps of anti-A/B antibodies have been removed with each plasma volume. We were able to remove 2.1 titer steps by treating the 2.2-fold plasma volume. TPE shows the same results, even with the treatment of 1.3-fold plasma volume. Asian centers mainly use TPE. In contrast to TPE, IA is highly selective and, as there is no substitution required, holds no transfusion complications. Still, Glycosorb columns are only for single use and cost-intensive. Unfortunately, during one procedure we cannot treat the plasma as often as needed to erase all antibodies from the blood. The amount of plasma we can treat is limited by the amount of citrate we have to administer to each plasma volume because the patient's compromised liver is very limited in metabolizing citrate.

The decision which type, duration, and frequency of PTP we have used has been individualized based on the initial titers, diagnosis, rebound, and response.

The HCC patients showed high initial titer and rebounded strongly (TI ≥ 2) despite immunosuppressant therapy (table 2). Investigations of Peter and Werny [30] indicate distinctly higher values of anti-A/B in patients with severe consuming and tumor diseases than in healthy blood donors. One hypothesis explaining the rebound is that the expression of blood group antigens on the biliary tree alters in pathological conditions [24]. The neoexpression or aberrant expression of A or B substances in malignant cells can boost the production of antibodies [25]. Therefore, the tumor bulk might define the antibody rebound. A big tumor mass could define on one hand a high initial antibody titer and on the other a strong rebound (TRR < TI). Due to their high pre-transplantation rebound, patient 5, 9 and 10 did not receive ABOi LDLT. Still patient 2, 4 and 8 were transplanted despite their rebound (fig. 1–3). Patient 4 and 8 developed severe complications after ABOi LDLT.

Fig. 1. Anti-A titers pre- and post-PTP are displayed. At transplantation the anti-A titer surprisingly increased significantly.

Fig. 2. Anti-B titers pre- and post-PTP are displayed. Between the days -1 and +1 antibodies rebounded with TI > TRR.

Fig. 3. Anti-A titers pre- and post-PTP are displayed. On day +1 after LDLT, TRR is equivalent to TI.

Another reason for high initial antibody titers will be immunization against A and B substances. This immunization hypothesis is supported by pediatric ABOi liver transplant recipients < 1-year-old having a higher post-transplant survival compared to recipients older than 16 years (76% vs. 22%) [26].

In our study anti-A/B rebound occurred mainly after 3 PTP or within 1 week after the first treatment. Additional PTP were necessary to overcome this rebound and achieve the required titer of 1:8

for the surgery day. Prior to ABOi LDLT, we performed on average 4 (1–7) PTP to achieve the target value in 50% of all cases.

Based on our present experience, currently we consider cancelling further scheduling for transplantation if TRR is below TI in HCC patients after 5 PTP. These patients are at high risk for arterial thrombosis and graft loss. Other transplant centers performed up to 12 PTP before transplantation. No upper limit of PTP has been reported so far [27].

Further, the necessity for splenectomy/anti-CD20 treatment to prevent post-transplantation antibody rebound is still debated. In contrast to Asian protocols, we performed all ABOi LDLTs without splenectomy and without anti-CD20 treatment. Anti-CD20 effectively eliminates CD20-positive B cells up to 6 months, but does not directly affect antibody-producing plasma cells. B cells residing in the lymph nodes stay unaffected by anti-CD20 and are activated by the ABOi graft. As a result, antibody production at low levels is still possible. De novo production of antibodies is sufficiently delayed due to anti-CD20 treatment [28–31]. We assume that splenectomy or anti-CD20 treatment combined with PTP and reinforced immunosuppression can lead to over-immunosuppression and severe systemic infections [1, 28]. In the study by Thorsen et al. [17], 44 of 66 patients deceased after ABOi LDLT despite anti-CD20 administration. Most Asian centers use protocols with anti-CD20, plasmapheresis, intravenous immunoglobulin (IVIG), local graft perfusion, and splenectomy [23]. But some Asian centers no longer perform splenectomy routinely [1, 8, 15]. Reports have shown that splenectomy does not offer any immunological benefit in ABOi LDLT. For example Raut et al. [32] observed no statistically significant differences in anti-A/B IgM as well as IgG antibody titers between the ‘splenectomy’ and the ‘non-splenectomy’ group. The clinical outcome, including AMR, biliary complications, infections and survival, was also similar in both groups.

Due to the risk of over-immunosuppression, lack of significant benefit and perioperative risks like pancreatic fistula, perioperative morbidity or sepsis, we see no indication for splenectomy. However, IVIG preparations have potent immunoregulatory qualities, too [33]. Urbani et al. [34] described one case of successful use of high-dose IVIG application in ABOi LDLT with AMR. Unfortunately, we observed a transient increase of anti-A/B titers following administration of IVIG and decided to cancel the administration of IVIG in ABOi LDLT treatment schedule. The European Pharmacopoeia recommends anti-A and anti-B to be undetectable in IVIG preparations at 1:64 dilutions [35]. The amount of anti-A/B varies in different preparations. Our own investigations show a variation from 1:1,024 to 1:16 for anti-A1 titer, from 1:256 to 1:4 for anti-A2, and from 1:256 to 1:8 for anti-B. IVIG infusion leads to a passive transfer of anti-A/B.

PTP are the only effective method to decrease antibody titers after ABOi LDLT [36]. In two cases we were able to save patient and graft with 11 or 12 PTP. Despite reinforced PTP twice a day, patient 4 suffered from hepatic necrosis and died.

Sanchez -Urdazpal et al. [6] reported in 1993 that biliary complication and rejection in deceased patients with ABOi LDLT was much higher than in deceased patients with ABOc LT. Biliary com-

plications were developed by 54–82% of the ABOi allograft recipients compared to 6% in ABO matched allografts. Hepatic artery thrombosis occurred in 24% of ABOi allografts [3, 28]. The meta-analysis of Wu et al. [2] in 2011 showed the total complication incidence and acute rejection incidence to be higher after ABOi LDLT than after ABOc LT. Lee et al. [23] performed ABOi LDLT with a protocol of plasmapheresis, IVIG, and quadruple immunosuppressive therapy (basiliximab, tacrolimus, mycophenolate mofetil, steroids). The authors reported that 5.6% of the patients developed complications like diffuse intrahepatic biliary strictures (DIHBS) which occurred 2.1–5.2 months post-transplant. The overall biliary complications may be related to direct immunological mechanisms such as bile duct epithelium expressing A and B blood group antigens [6, 7]. Song et al. [15] also reported a higher incidence of biliary strictures in ABOi LDLT due to DIHBS than in ABOc transplantations. These strictures affected the overall survival significantly.

Living donation provides a curative treatment option for patients with HCC cirrhosis, particularly if a patient is not offered a donor organ by Eurotransplant. This can be due to low labMELD or a tumor burden above the Milan criteria, even if it has benign tumor biology. There are only a few reports on successful ABOi LDLT for patients with HCCs outside Milan criteria [37]. Because of a high early recurrence rate of 57% in the first year after ABOi LDLT, Lee et al. [38] recommended not to treat HCC patients with

ABOi LDLT. In our series, we transplanted 4 HCC patients (1 outside, 3 inside Milan criteria). The ‘outside’ patient developed pulmonary metastases within 1 year after ABOi LDLT.

Conclusion

Anti-CD20 treatment is a known option and possibly influences antibody rebound after transplantation. ABOi LDLT without anti-CD20 administration is possible as well, if the primary disease’s escalation or severe side effects are feared. In our facility, we have combined PTP and quadruple drug immunosuppression. However, 5 of 6 patients are still in hold of their first transplanted organ after 3 years.

In this study, patients with HCC and a TRR below TI were at high risk for arterial thrombosis and graft loss. These patients should be cancelled for further scheduling.

It remains questionable how transplant risks for HCC patients are to be lowered and how immunosuppression and PTP can be adjusted to overcome the strong rebound prior to transplantation.

Disclosure Statement

The authors declare no conflict of interest.

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