Case report

ABO-incompatible living donor liver transplantation with high preoperative antibody titer: A case report

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A B S T R A C T

Introduction and importance: ABO-incompatible living donor liver transplantation (ABOi-LDLT) is essential for expanding the donor pool. ABOi-LDLT prognosis has improved since desensitization treatment with rituximab; however, patients with high antibody titers are considered to be at high risk of antibody mediated rejection (AMR). Nevertheless, the preoperative antibody titer cutoff levels that preclude ABOi-LDLT have not yet been determined. In this study, the highest preoperative antibody titer was 1:4096, and the recipient had good outcomes. There has been only one report of good outcomes with a preoperative antibody titer of more than 1:4096. We hypothesized that high preoperative antibody titers in ABOi-LDLT may not be associated with AMR in protocols involving rituximab.
Case presentation: The recipient was a 22-year-old man with biliary atresia and underwent ABOi-LDLT (B to O). We administered 500 mg of rituximab 14 days prior and then 300 mg of rituximab one day prior to ABOi-LDLT. The recipients preoperative IgG antibody titer was 1:4096. Postoperative immunosuppressive protocol involved steroids, tacrolimus, and mycophenolate mofetil. The patient had satisfactory graft function three years following ABOi-LDLT.
Clinical discussion: The antibody that is responsible for posttransplant AMR should be newly synthesized after transplantation as a result of sensitization by antigens on the vascular endothelial cells of the graft. In ABOi-LDLT, natural antibodies may not cause AMR.
Conclusions: The most important factor for preventing AMR in recipients undergoing ABOi-LDLT is the suppression of de novo antibodies. High preoperative antibody titers may not necessarily preclude ABOi-LDLT, provided that rituximab is used in desensitization.

1. Introduction

Liver transplantation is a suitable treatment option for patients with end-stage liver disease [1,2]. In cultural settings where brain-dead donor liver transplants are uncommon, ABO-incompatible living donor liver transplantation (ABOi-LDLT) is essential to expand the donor pool [3,4]. Previously, ABOi-LDLT had poor prognosis due to antibody-mediated rejection (AMR) that was consequently considered a contraindication [5]. ABOi-LDLT prognosis has dramatically improved since the development of desensitization treatment with rituximab [6]. However, patients with high antibody titers are considered to be at a higher risk of AMR than those with low antibody titers [7]. Plasma exchange (PE) has been reported to rapidly reduce blood antibody titers. In addition, repeated PE has been preoperatively used in patients with high

antibody titers to reach a titer level considered safe to perform ABOi-LDLT [8,9]. Nevertheless, the preoperative antibody titer cut-off level that precludes ABOi-LDLT has not yet fully elucidated. Moreover, whether preoperative antibody titer is related to AMR frequency remains controversial. We hypothesized that AMR is caused by posttransplant de novo antibodies and may not be related to natural antibodies present in the recipient before ABOi-LDLT. In this study, the highest preoperative antibody titer was 1:4096, and repeated PE was ineffective, with reductions in the preoperative antibody titers to only 1:256. Nevertheless, the recipient had a good outcome and satisfactory graft function three years postoperatively. This case was reported in line with the SCARE criteria [10].

2. Case presentation

The patient was a 22-year-old man with congenital biliary dilatation who had previously undergone biliary reconstruction at the age of 1 month. However, he experienced recurrent cholangitis. Consequently, he underwent a second biliary reconstruction at the age of 16 years. Thereafter, his liver became cirrhotic due to cholangitis. The recipient had no history of smoking, alcohol, or recreational drug. At 22 years of age, the patient was scheduled to undergo liver transplantation. The only donor available was his mother, a 47-year-old woman. However, their blood groups were incompatible (B to O). The recipient's preoperative immunoglobulin G (IgG) anti-B antibody titer was 1:4096. The recipient was started on a preconditioning desensitization protocol with rituximab, antibody removal using plasma exchange (PE), immunosuppression therapy with tacrolimus, basiliximab and mycophenolate mofetil (MMF) administration, as previously described (Fig. 1) [11]. He was administered 500 mg of rituximab two weeks before LDLT and 0.075 mg/kg/day of tacrolimus five days before LDLT. Tacrolimus trough levels were maintained at 5–8 ng/mL until transplantation, and MMF was administered at a dose of 500 mg twice daily during the week before LDLT. Although PE was performed five times, the IgG antibody titers one day prior to transplantation were 1:256. Consequently, we preoperatively administered 300 mg of rituximab (Fig. 2). No adverse reactions were observed during the course of treatments.

The surgical procedure for transplantation was performed as previously described [12,13]. The weight of the right lobe graft was 570 g, and the graft to recipient weight ratio was 1.0. V8, which is a venous branch from the middle hepatic vein to the segment, was reconstructed using the recipient's superficial femoral vein, forming the joint with the right hepatic graft vein (Fig. 3a). Splenectomy was performed (Fig. 3b). The postoperative protocol was as follows: tacrolimus was administered to maintain trough levels of 10–12 ng/mL for 14 days and of 8–10 ng/mL after 14 days; 500 mg of MMF was administered twice daily; 200 mg of methylprednisolone (MP) was administered on postoperative day (POD) 1, 160 mg on POD 2, and 125 mg on POD 3. The MP dose was subsequently tapered to 8 mg once daily for one month. As the IgG antibody titer was 1:256 on POD 6, PE was performed; however, the IgG titers rebounded to 1:512 on POD 9 (Fig. 4a). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels decreased on POD 9 (78 U/L and 84 U/L, respectively) (Fig. 4b). We performed steroid pulse treatment, which included 500 mg/day of MP, for 2 days. In total, PE was performed five times postoperatively, yet the IgG titer rebounded to 1:512 on POD 9. The IgM antibody titer was maintained at approximately 1:4, and AST and ALT levels improved. CD19-positive
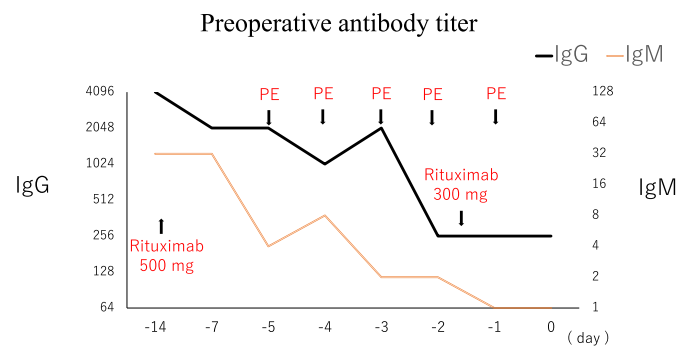

Fig. 2. Changes in antibody titers before ABO-incompatible living donor liver transplantation (ABOi-LDLT)PE was performed five times prior to LDLT. PE, plasma exchange.

cells in the recipient were controlled to 1.8% for 2 months after rituximab administration. The recipient was discharged on POD 46 and had good graft function three years following transplantation.

3. Anti-ABO antibody titer monitoring

IgG and IgM antibody titers were measured using a tube test. Anti-A and anti-B antibody titers of IgM were determined by diluting the patient's untreated plasma, mixing the plasma with a sample of A or B blood cells, and subsequently centrifuging for 15 s. The IgG antibody titer was determined by the indirect globulin method. The plasma in which the IgM components were inactivated by treatment with dithiothreitol was diluted, and the sample of A or B blood cells was mixed and reacted at 37 °C for 60 min. Blood cells were subsequently washed 3 times, centrifuged for 15 s, and agglutinated. The reaction was graded macroscopically, with the highest dilution showing +1 agglutination.

4. Discussion

Some countries, including Japan, have a low rate of liver grafts from brain-dead donors [2]. Instead, living donor liver transplantations are frequently performed. Since donors are limited to close relatives for ethical reasons, donors and recipients are often blood type-incompatible. ABOi-LDLT is needed as a treatment option to expand the donor pool in regions with severe donor organ shortages. Although the outcome of ABOi-LDLT was not as good as that of ABO-compatible LDLT previously [5], it has improved since the introduction of various
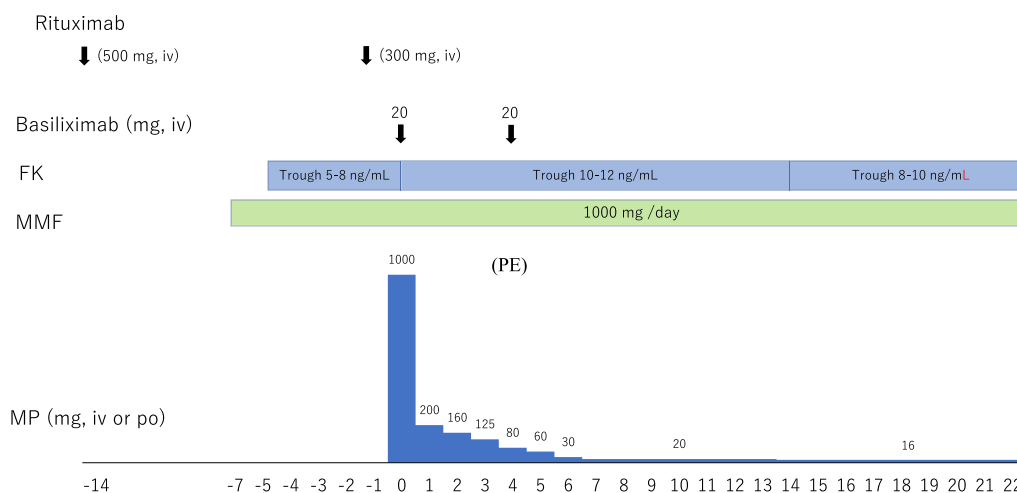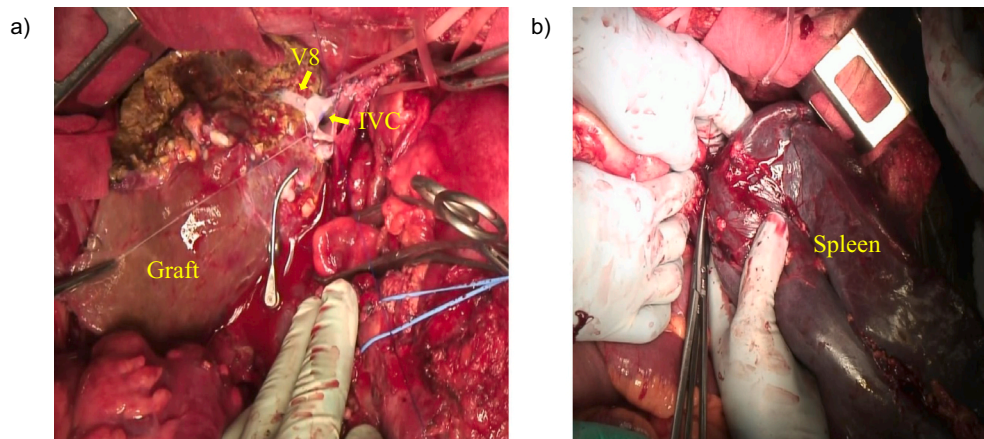

Fig. 1. Perioperative protocol of desensitization treatment with rituximab, plasma exchange (PE), and immunosuppressants IV, intravenous; FK, tacrolimus; MMF, mycophenolate mofetil; MP, methylprednisolone; and PO, per os.

Fig. 3. Main surgical procedures a) GRWR was 1.0. TV8 was reconstructed using the recipient's superficial femoral vein, forming the joint with the right hepatic vein of the graft. b) Splenectomy was performed. GRWR, Graft to recipient weight ratio. V8, A venous branch from the middle hepatic vein to the segment.
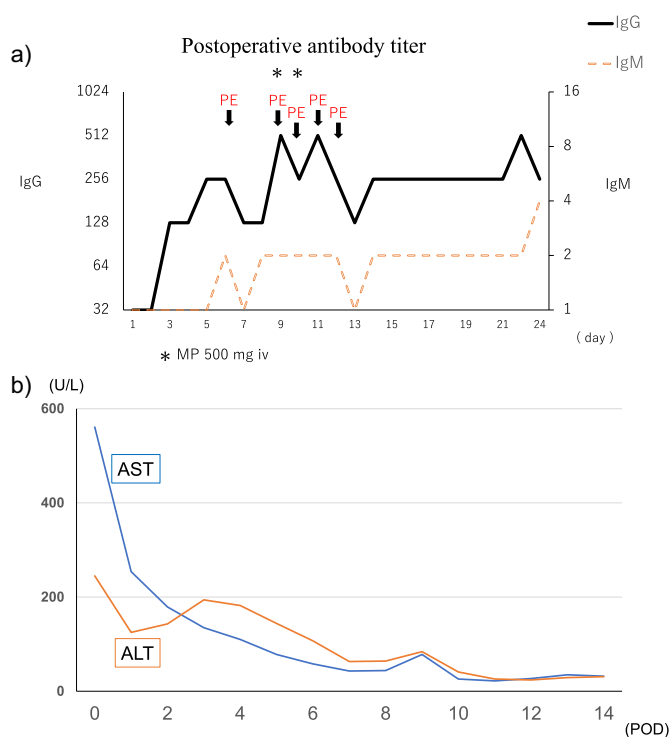
Fig. 4. a) Changes in antibody titers after ABOi-LDLTOn postoperative day 6, PE was performed, yet the immunoglobulin G titer rebounded to 1:512 on postoperative day 9. Steroid pulse treatment, which included 500 mg/day of methylprednisolone, was performed on postoperative days 9 and 10. The immunoglobulin M antibody titer was maintained at approximately 1:4. b) AST and ALT levels improved rapidly after ABOi-LDLTIV, intravenous; MP, methylprednisolone; PE, plasma exchange; AST, aspartate aminotransferase; and ALT, alanine aminotransferase.

treatments, including: PE, local infusion, splenectomy, and especially rituximab desensitization [6,14]. Rituximab is a monoclonal anti-CD20 antibody that depletes B cells by complement-dependent cellular cytotoxicity [1]. It also depletes CD20-positive B cells from circulation and lymphoid tissues. Previous studies have shown that rituximab's effect on B cells in peripheral blood removes cells within 72 h [6]. Even after the introduction of rituximab, patients with high preoperative antibody titers are considered to be at a higher risk of AMR than those with low antibody titers. Egawa et al. reported that AMR frequency was significantly higher in patients with a preoperative IgG titer >1:128 compared

to those with a titer lower than this level [7]. However, it is controversial whether the antibodies present in the recipient prior to transplantation could cause AMR. Takahashi et al. reported that, in ABO-incompatible kidney transplantation, pretransplant desensitization therapy to suppress host B cell immunity against ABO histo-blood group antigens would be the most effective treatment to ensure successful outcomes. [15].

It was conventionally believed that AMR was caused by natural antibodies present in the recipient. Nevertheless, it was clear that the antibodies eliciting AMR were not produced without graft transplantation, meaning that the recipient should be sensitized to the ABO histo-group antigens on the vascular endothelial cells of the donor graft, causing the novel production of de novo antibodies. The antibody that is responsible for posttransplant ABO-related AMR should be newly synthesized after transplantation as a result of sensitization by ABO histo-group antigens on the vascular endothelial cells of the graft. Anti-ABO blood group antibodies and anti-ABO histo-group antibodies are similar, but have strictly different structures [15]. De novo antibodies synthesized after transplantation cause AMR [16]. This theory has been reported based on findings of ABO-incompatible kidney transplantation. However, it is also universal and applicable to liver transplantation as well. We hypothesized that high preoperative antibody titers in ABOi-LDLT may not be associated with AMR in protocols where the production of de novo antibodies is strongly suppressed by rituximab. Actually, since the introduction of rituximab, AMR has rarely been reported [17]. Several studies have reported that high preoperative antibody titers are not significantly correlated with AMR incidence. Skogsberg et al. performed ABOi-LDLT in 12 patients with preoperative antibody titers up to ≥1:1024 and concluded that there was no correlation between AMR risk and antibody titers [18]. Shen et al. reported that 5.7% of recipients were diagnosed with AMR after ABOi-LDLT. However, AMR is not directly associated with a higher level of anti-ABO antibody titer preoperatively [19]. Based on these discussions, the suppression of de novo antibody production by rituximab is most important for preventing graft loss due to AMR.

This study has several limitations. ABOi-LDLT is a treatment that should have been subjected to ethical debate in that it is invasive to healthy donors. In cultures with sufficient brain-dead donors for patients on the waiting list, LDLT should not be routinely recommended. The extent to which high cut-off levels of preoperative antibody titers for ABOi-LDLT are acceptable cannot be determined based on this study alone. However, other than this study, the only report of a good outcome with ABOi-LDLT at preoperative antibody titers of more than 1:4096 is that of Shimoda et al. (1:8192) [20]. Extensive studies are needed to save patients in need of transplantation in cultures where brain-dead donors are limited. In this study, PE and splenectomy were performed

in favor of immunological benefits. However, these procedures may result in some complications in recipients [21], and their indications need to be discussed.

5. Conclusion

The most important factor for preventing graft loss due to AMR in patients undergoing ABOi-LDLT is the suppression of de novo antibodies. Desensitization therapy with rituximab strongly suppresses de novo antibody production. Antibodies present in the recipient prior to transplantation may have not been involved in AMR. We reported a case of good prognosis after ABOi-LDLT with a high preoperative IgG titer of 1:4096. We suggest that high preoperative antibody titers may not be considered a limitation to ABOi-LDLT when protocols that include rituximab desensitization are used.

Ethics approval

This study was approved by the ethics committee of Tohoku University Hospital.

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CRediT authorship contribution statement

Yoshikatsu Saitoh is a major contributor in writing the manuscript. Atsushi Fujio, Shigehito Miyagi, and Kazuaki Tokodai were attending doctors who performed clinical treatment, including surgical operation. All authors have read and approved the final manuscript.

Guarantor

Yoshikatsu Saitoh

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

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Declaration of competing interest

The authors declare no conflicts of interest.

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