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Overcoming ABO Blood Type Incompatibility in Living Donor Liver Transplantation

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ABSTRACT

Introduction : The hurdle of ABO blood-type incompatibility (ABOi) needs to be overcome in living donor liver transplantation (LDLT).

Methods : On the basis of a desensitization protocol for ABOi LDLT, we have administered rituximab (500 mg/body), an anti-CD20 antibody, followed by possible plasma exchange, to patients 3 weeks before undergoing LDLT.

Results : Four patients with end-stage liver disease received rituximab 3 to 4 weeks before undergoing LDLT, followed by plasma exchange in 2 patients, resulting in no rebound elevation of the isoagglutinin titers after LDLT. Lymphocytes positive for CD20 at the time of LDLT were evaluated in 3 recipients and were decreased in all 3 patients to less than 1.0%. The isoagglutinin titers of the 4 patients before desensitization, before LDLT, and 6 months after LDLT, respectively, were 64, 64, and 1 ; 128, 64, and 4, 32, 32, and 2 ; and 64, 1, and 1. Two patients received right lobe grafts, and the other 2 patients received left lobe grafts. One patient had acute cellular rejection, which was successfully treated with corticosteroid treatment, and no patient had antibody mediated humoral rejection after LDLT. The 4 patients are alive 59, 54, 39, and 9 months after ABOi LDLT with controlled liver function.

Conclusions : The rituximab-based ABOi desensitization protocol for LDLT appears to be a safe and effective treatment method and might expand the donor pool.

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Key words : living donor liver transplantation, blood type incompatibility, rituximab, perioperative management

INTRODUCTION

Living donor liver transplantation (LDLT) has become an optional treatment for patients with end-stage liver disease, especially in such Asian countries as Japan, South Korea, Taiwan, and Hong Kong[1]. However, LDLT is performed less often than necessary because of the limited number of appropriate living donors[2]. Because the number of deceased donors is also limited, LDLT is occasionally performed with ABO blood type incompatibility (ABOi) grafts[3-6]. Despite the poor outcomes in the initial series of ABOi LDLT, local infusion treatment with protease inhibitors, prostaglandins, and corticosteroids increases recipient survival[3,4]. Nevertheless, the local administration of such agents can be associated with a high incidence of catheter-associated problems, such as hepatic hilar vascular thrombosis and or

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intra-abdominal bleeding. An anti-CD20 monoclonal antibody agent that specifically targets the CD20 surface antigen expressed on B-lymphocytes is rituximab[5-9]. Rituximab has been shown to induce complement-mediated cell lysis on CD20-positive cells and antibody-dependent cell cytotoxicity[5,10,11]. The use of rituximab to prevent rejection in ABOi LDLT was first reported in 2007[5].

We have introduced ABOi LDLT with a rituximab desensitization protocol, and, therefore, in the present study we reviewed outcomes and complications in a series of patients who have undergone ABOi LDLT.

MATERIALS AND METHODS

Since 2004, 24 patients have undergone LDLT at The Jikei University Hospital. Of these patients, 4 underwent ABOi LDLT. All LDLTs were performed after full informed consent had been obtained from the patients and the Liver Transplantation Committee of The Jikei University School of Medicine had approved. The basic surgical procedures and techniques for the donors and recipients have been previously described[12,13]. Because of the small graft size (graft volume/standard liver volume ratio < 60%), splenectomy was performed before LDLT in all patients.

The basic immunosuppression regimen for LDLT included tacrolimus with mycophenolate mofetil and corticosteroids. Before LDLT, mycophenolate mofetil was administered at a dose of 2 g/day for 7 days. After LDLT, tacrolimus was administered when the estimated glomerular filtration rate was > 30 ml/minute. The target tacrolimus level ranges from 10 to 15 ng/ml for the first month after LDLT and is titrated from 10 to 7 ng/ml during the next several months. Methylprednisolone is administered at a dose of 20 mg/kg after reperfusion, tapered from 10 to 1 mg/kg over 7 days, and replaced with oral prednisolone at an initial dose of 20 mg/kg, which was tapered to 0, for 6 months after LDLT. For fungal infection prophylaxis, intravenous micafungin was administered for 7 days after LDLT and followed with oral amphotericin B at a dose of 300 mg/day.

Rituximab (500 mg/body) was administered 3 weeks before the scheduled LDLT for patients with chronic liver diseases[8,9]. The isoagglutinin titer before LDLT was measured with an immunoglobulin G assay[14]. For recipients with an isoagglutinin titer > ×64, flow cytometry was performed at least 2 weeks before LDLT to confirm the rate of CD20-positive cells. To decrease the isoagglutinin titer before LDLT to < ×64, plasma exchange was performed with fresh frozen plasma[7]. Plasma exchange with possible high-dose intravenous immunoglobulin (IVIG) was also ready for use after LDLT if a patient showed antibody-mediated rejection (AMR) with elevated liver enzymes and a progressive increase of isoagglutinin titers. If patients had pathological evidence of acute cellular rejection (ACR), methylprednisolone was administered at a dose of 1 gram for 2 consecutive days, tapered from 200 mg to 40 mg over 5 days, and then replaced with 20 mg of oral prednisolone under the prophylactic administration of ganciclovir to prevent cytomegalovirus infection.

This retrospective study complies with the Declaration of Helsinki and was approved by the Ethics Committee of The Jikei University School of Medicine (protocol ID number 27-177) with waiver of informed consent.

RESULTS

The 4 patients who underwent ABOi LDLT had a mean recipient age of 56.8 ± 3.3 years (Table 1). Primary liver diseases for LDLT included primary biliary cirrhosis for 2 patients, primary biliary cirrhosis with hepatocellular carcinoma for 1 patient, and cryptogenic liver cirrhosis with hepatocellular carcinoma for 1 patient. The mean model for the end-stage liver disease score[1,7,16] was 10.3 ± 2.6. Blood type combinations of donors to recipients included B to A for 2 patients, AB to A for 1 patient, and A to O for 1 patient. The mean age of donors was 56.7 ± 1.0 years. The graft types included extended left lobe grafts with middle haptic vein and caudate lobe (2 patients) from the husband of female recipients and right lobe grafts (2 patients) from the sisters of the female recipients. The mean graft volume was 494 ± 84 g, and the graft volume standard liver volume ratio was 46.2% ± 8.7%.

All patients received rituximab before LDLT (Table 2). Plasma exchange was performed 3 times in 2 recipients and effectively decreased the isoagglutinin titers before LDLT. Lymphocytes positive for CD20 at the time of LDLT were evaluated in 3 recipients with high initial isoagglutinin titers. In these 3 recipients the CD20-positive cells were decreased to less than 1.0% of all lymphocytes. The isoagglutinin titers in the 4 recipients before desensitization, before LDLT, and 6 months after LDLT, respectively, were 64, 64,

Table 1. Recipient and donor information

Patient	Recipient				Donor					
	Age / Sex	Primary disease	MELD	ABO	Age / Sex	ABO	Relationship	Graft	Graft volume (g)	Graft volume standard liver volumes ratio
1	53 F	PBC	14	A	55 M	B	Husband	LL	446	40.6%
2	65 F	PBC HCC	10	A	58 F	B	Sister	RL	597	57.1%
3	55 F	LC HCC	13	A	58 M	AB	Husband	LL	332	30.2%
4	54 F	PBC	4	O	56 F	A	Sister	RL	604	57.1%

ABOi, ABO incompatible ; HCC, hepatocellular carcinoma ; LC, liver cirrhosis ; LL, left lobe ; MELD, model for end stage liver disease ; PBC, primary biliary cholangitis ; RL, right lobe

Table 2. Desensitization protocol and outcomes

Patient	Rituximab (Pre-LDLT day)	PE	Isoagglutinin titer				CD20-positive cell	Splenectomy	Rejection	Operation time (min)	EBL (g)	LHS (days)	BTF			Outcomes
			Initial (day)	at LDLT	1 mo	6 mo							RBC (u)	FFP (u)	PC (u)	
1	Yes (27)	-	64 (day-27)	64	1	1	0.1%	Yes	ACR (day 8, corticosteroid)	718	1,950	42	4	0	0	Alive 59 months
2	Yes (20)	×3	128 (day-32)	64	4	4	0.5%	Yes	No	776	2,050	30	4	16	10	Alive 54 months
3	Yes (21)	-	32 (day-29)	32	1	2	-*	Yes	No	815	3,590	33	22	20	10	Alive 39 months
4	Yes (21)	×3	64 (day-28)	1	16	1	0.7%	Yes	No	1,130	2,160	35	8	16	20	Alive 9 months

ACR, acute cellular rejection ; BTF, blood transfusion ; EBL, estimated blood loss ; FFP, fresh frozen plasma ; LDLT, living donor liver transplantation ; LHS, length of hospital stay ; PC, platelet concentrates ; PE, plasma exchange ; RBC, red blood cell
*Flow cytometry to detect CD20-positive cells was not performed.

and 1 ; 128, 64, and 4 ; 32, 32, and 2 ; and 64, 1, and 1. No adverse events after rituximab administration were observed in any patient. Two recipients received right lobe grafts, and the other 2 recipients received left lobe grafts. One patient had ACR successfully treated with corticosteroid treatment, and no patient had AMR after LDLT. All 4 patients are alive 59, 54, 39, or 9 months after ABOi LDLT with controlled liver function. All donors were discharged without severe complications.

Discussion

Despite the unsatisfactory outcomes of ABOi LDLT previously reported, trials of methods to increase the survival rate have been performed in Japan, where the chance of acquiring liver grafts from deceased donors is low[1,2]. The first significant advance in performing ABOi LDLT was graft local infusion treatment, including the intraportal or intra-arterial infusion of prostaglandin E1, mesylate gabexate, and methylprednisolone[3,4]. Although this treatment improved the results of ABOi LDLT, its problems included catheter-associated complications[3,4]. However, this treatment also greatly increased the graft survival rate after ABOi LDLT[3-5].

The transmembrane polypeptide CD20 is expressed on the majority of both normal and malignant B cells and is an appropriate target for monoclonal antibody therapy[15]. Rituximab, the first monoclonal antibody to be approved for therapeutic use in 1997, is a monoclonal gamma globulin that binds to CD20 on the surfaces of both normal and malignant B cells and destroys these cells. Although rituximab was initially used exclusively for B cell lymphomas, previous trials have described its use in various immune-related diseases, including systemic lupus erythematosus and rheumatoid arthritis[11,16]. Rituximab has been reported to reduce the peak immunoglobulin G isoagglutinin titers in ABOi LDLT recipients[9] ; therefore, immunoglobulin G assays are considered important for ABOi LDLT.

Early reports of ABOi LDLT described its ineffectiveness for controlling the rebound elevation of the isoaggluti-

nin titer and the occurrence of total graft necrosis with its use after LDLT[3].

However, its use as long as 3 weeks before the LDLT has been reported to achieve successful outcomes[5]. Furthermore, the administration of rituximab earlier than 7 days before LDLT has been reported to significantly deplete CD20-positive B lymphocytes and memory B lymphocytes and to decrease the peak post-LDLT isoagglutinin titers and that rituximab administered 3 weeks before LDLT depleted B-cells[14]. A national study has reported that a single regular dose of rituximab (500 mg/body or 375 mg/m^2) has a lower incidence of AMR than does a single smaller dose (300 mg/body) and that multiple doses of rituximab significantly increase the incidence of fungal and viral infections. Other reported adverse effects of rituximab include renal dysfunction, sepsis, neutropenia, lung edema, and anaphylaxis[14]. Plasma exchange is indicated when the isoagglutinin titer is greater than ×64. In a previous study[7] 2 to 8 sessions of plasma exchange were required to reduce isoagglutinin titer to ×64. However, in the present study, isoagglutinin titers in 2 patients were successfully reduced with 3 sessions of plasma exchange, respectively. Those desensitization protocol using rituximab has improved outcomes after LDLT, and graft and patient survival rates did not differ significantly between recipients of ABOi and ABO compatible LDLT in the propensity score-matched analysis[17]. A major complication of ABOi LDLT is AMR, which mainly occurs within 2 years after LT and significantly decreases the overall survival rate[14]. Because AMR might occur, we have prepared corticosteroid pulse treatment with 2 sessions of methylprednisolone at an initial dose of 1 gram, which is then tapered, and plasma exchange to decrease the isoagglutinin titer with high-dose IVIG. In a similar way, IVIG has been effectively used to control acute humoral rejection in highly sensitized candidates for kidney transplantation[18-20]. The proposed mechanisms of action of IVIG on the humoral reaction include B-cell apoptosis through the Fc-receptor dependent pathway and the inhibition of T-cell–mediated or complement-mediated allograft injury ; however, these possible mechanisms have not been confirmed. A possible third line for treating AMR is the use of newly developed drugs, including bortezomib to suppress plasma cells and eculizumab to control C5 complement system could be the as recently reported[21,22]. Of the present patients, only 1 (patient 1 in Tables 1 and 2) had ACR after LDLT. Because ACR was thought to be T cell-mediated rejection, we suggest plasma exchange before LDLT to reduce isoagglutinin titer in this patient could not prevent ACR.

In conclusion, ABOi LDLT could be safely performed under a rituximab-based protocol to effectively prevent AMR.

Authors have no conflicts of interest.

REFERENCES

1. Tanaka K, Uemoto S, Tokunaga Y, Fujita S, Sano K, Nishizawa T, et al. Surgical techniques and innovations in living related liver transplantation. Ann Surg. 1993 ; 217 : 82-91.
2. Kubota T, Hata K, Sozu T, Ueda Y, Hirao H, Okamura Y, et al. Impact of Donor Age on Recipient Survival in Adult-to-Adult Living-donor Liver Transplantation. Ann Surg. 2018 ; 267 : 1126-1133.
3. Tanabe M, Shimazu M, Wakabayashi G, Hoshino K, Kawachi S, Kadomura T, et al. Intraportal infusion therapy as a novel approach to adult ABO-incompatible liver transplantation. Transplantation. 2002 ; 73 : 1959-61.
4. Egawa H, Teramukai S, Haga H, Tanabe M, Fukushima M, Shimazu M. Present status of ABO-incompatible living donor liver transplantation in Japan. Hepatology. 2008 ; 47 : 143-52.
5. Usui M, Isaji S, Mizuno S, Sakurai H, Uemoto S. Experiences and problems pre-operative anti-CD20 monoclonal antibody infusion therapy with splenectomy and plasma exchange for ABO-incompatible living-donor liver transplantation. Clin Transplant. 2007 ; 21 : 24-31.
6. Egawa H, Ohdan H, Haga H, Tsuruyama T, Oike F, Uemoto S, et al. Current status of liver transplantation across ABO blood-type barrier. J Hepatobiliary Pancreat Surg. 2008 ; 15 : 131-8.
7. Ikegami T, Taketomi A, Soejima Y, Yoshizumi T, Uchiyama H, Harada N, et al. Rituximab, IVIG, and plasma exchange without graft local infusion treatment : a new protocol in ABO incompatible living donor liver transplantation. Transplantation. 2009 ; 88 : 303-7.
8. Soejima Y, Muto J, Matono R, Ninomiya M, Ikeda T, Yoshizumi T, et al. Strategic breakthrough in adult ABO-incompatible living donor liver transplantation : preliminary results of consecutive seven cases. Clin Transplant. 2013 ; 27 : 227-31.
9. Egawa H, Ohmori K, Haga H, Tsuji H, Yurugi K, Miyagawa-Hayashino A, et al. B-cell surface marker analysis for improvement of rituximab prophylaxis in ABO-incompatible adult living donor liver transplantation. Liver Transpl. 2007 ; 13 : 579-88.
10. Ikegami T, Taketomi A, Soejima Y, Iguchi T, Sanefuji K, Kayashima H, et al. Successful ABO incompatible living donor liver transplantation in a patient with high isoagglutinin titer using high-dose intravenous immunoglobulin. Transplant Proc.

2007 ; 39 : 3491-4.
11. Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody : history and mechanism of action. Am J Transplant. 2006 ; 6 : 859-66.
12. Ikegami T, Shirabe K, Yamashita Y, Yoshizumi T, Harimoto N, Takeishi K, et al. Small upper midline incision for living donor hemi-liver graft procurement in adults. J Am Coll Surg. 2014 ; 219 : e39-43.
13. Ikegami T, Soejima Y, Taketomi A, Yoshizumi T, Harada N, Uchiyama H, et al. Explanted portal vein grafts for middle hepatic vein tributaries in living-donor liver transplantation. Transplantation. 2007 ; 84 : 836-41.
14. Egawa H, Teramukai S, Haga H, Tanabe M, Mori A, Ikegami T, et al. Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation : a Japanese multicenter study. Am J Transplant. 2014 ; 14 : 102-14.
15. Johnson P, Glennie M. The Mechanisms of action of rituximab in the elimination of tumor cells. Semin Oncol. 2003 ; 1(Suppl 2) : 3-8.
16. Cartron G, Watier H, Golay J, Solal-Celigny P. From the bench to the bedside : ways to improve rituximab efficacy. Blood. 2004 ; 104 : 2635-42.
17. Song GW, Lee SG, Hwang S, Kim KH, Ahn CS, Moon DB, et al. ABO-incompatible adult living donor liver transplantation under the desensitization protocol with Rituximab. Am J Transplant. 2016 ; 16 : 157-70.
18. Sonnenday CJ, Warren DS, Cooper M, Samaniego M, Haas M, King KE, et al. Plasmapheresis, CMV hyperimmune globulin, and anti-CD20 allow ABO-incompatible renal transplantation without splenectomy. Am J Transplant. 2004 ; 4 : 1315-22.
19. Jordan SC, Vo AA, Peng A, Toyoda M, Tyan D. Intravenous gammaglobulin (IVIG) : a novel approach to improve transplant rates and outcomes in highly HLA-sensitized patients. Am J Transplant. 2006 ; 6 : 459-66.
20. Glotz D, Antoine C, Julia P, Suberbielle-Boissel C, Boudjeltia S, Fraoui R, et al. Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIg). Am J Transplant. 2002 ; 2 : 758-60.
21. Paterno F, Shiller M, Tillery G, O'Leary JG, Susskind B, Trotter J, et al. Bortezomib for acute antibody-mediated rejection in liver transplantation. Am J Transplant. 2012 ; 12 : 2526-31.
22. Marks WH, Mamode N, Montgomery RA, Stegall MD, Ratner LE, Cornell LD, et al. Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy : A randomized trial. Am J Transplant. 2019 ; 19 : 2876-88.