The changes in treatment strategies in ABOi living donor liver transplantation for acute liver failure

Mitsuhiro Yasuda, Toru Ikegami, Daisuke Imai, Huanlin Wang, Yuki Bekki, Shinji Itoh, Tomoharu Yoshizumi, Yusuke Soejima, Ken Shirabe, and Yoshishiko Maehara

Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Abstract: Introduction. Living donor liver transplantation (LDLT) using ABO-incompatible (ABOi) graft for acute liver failure (ALF) is a developing treatment modality. Methods. We reviewed the changes in our treatment strategies in applying ABOi-LDLT for FH over our fourteen years of experience. Results. Five patients with ALF received LDLT in adults using ABOi grafts, with different but gradually renewed protocols. The etiologies for acute liver failure included autoimmune hepatitis (n=3) and unknown (n=2). The desensitization protocol for ABOi barrier included Case #1: local infusion (portal vein)+plasma exchange (PE), Case #2: local infusion (hepatic artery)+rituximab+PE, Case #3 and #4: rituximab+PE, and Case #5: rituximab+PE under high-flow continuous hemodiafiltration. Local infusion was abandoned since Case #3, because Case #1 had portal vein thrombosis resulting in graft necrosis and Case #2 had hepatic artery dissection. The patients (Case #2 and #3), who received rituximab within 7 days before LDLT, experienced antibody-mediated rejection. Thus, the most recent protocol for ABOi-LDLT is that rituximab is given 2 weeks before LDLT, followed by high-flow continuous hemodiafiltration. Conclusion. Rituximab-based ABOi-LDLT, most-recently under high-flow hemodiafiltration for treating encephalopathy, is a feasible option for applying LDLT for ALF. J. Med. Invest. 62: 184-187, August, 2015

Keywords: living donor liver transplantation, blood type incompatible, acute liver failure, rituximab, high-flow continuous hemodiafiltration.

INTRODUCTION

Although living donor LT (LDLT) has now become an option for treating patients with end-stage liver disease, its application may still be limited by the need for an appropriate living donor (1,2). Under these circumstances, ABO incompatible (ABOi) LDLT has been practiced in Japan with recently improved outcomes by the recent invention and application of rituximab, a novel anti-CD20 antibody terminating B-lymphocytes (3).

In applying rituximab in LDLT, however, it needs to be administered at least a few weeks before LDLT for its desirable effects. It is attributed that rituximab rituximab can only terminate CD-20 positive B-lymphocytes and it takes at least a few weeks to CD-20 negative plasma cells to disappear spontaneously (4, 5). Thus, the application of ABOi-LDLT in emergent situation including acute liver failure (ALF) has not been a suitable option. In order to overcome this issue, we reported that high dose intravenous immunoglobulin (IVIG) was effective for treating antibody-mediated rejection (AMR) caused by remnant plasma cells after administration of rituximab (5). Progression of hepatic coma is the most significant determining prognostic factor in ALF, and therefore we recently started to use high-flow continuous hemodiafiltration (HF-CHDF) to treat hepatic coma and wait ABOi-LDLT for days to weeks after administration of rituximab (6).

In this article, we describe the historical changes in treatment strategies in applying ABOi-LDLT for ALF as a single institute experiences.

MATERIALS AND METHODS

Patients

Between May 1997 and December 2014, 486 LDLTs in adults including 30 LDLTs using ABOi grafts were performed at Kyushu University Hospital, Japan. Among them, 5 patients received ABOi LDLT for acute liver failure (Table 1). All the LDLTs were performed after obtaining full informed consent from all patients and approval by the Liver Transplantation Committee of Kyushu University. The basic surgical procedures and techniques were described previously (1, 7, 8). All 5 patients received duct-to-duct biliary reconstruction. The mean follow-up period was 3.8±3.7 years.

Basic immunosuppression

The basic immunosuppression induction regimen in ABOi LDLT involved the administration of tacrolimus (Tac) with mycophenolate mofetil (MMF) and steroids (Table 2). Currently, MMF is started 7 days before LDLT at a dose of 2 g/day, and increased to 3 g/day after LDLT, then decreased to 2 g/day once the blood calciurein inhibitor level reaches an appropriate level. Tac is started within 3 days after LDLT once the kidney function has recovered. The target Tac level ranges between 12 to 15 ng/ml for the first post-LDLT month and is titrated down to 8 to 10 ng/ml for the next few months. When patients experience Tac associated complications, especially encephalopathy, Tac is converted to Cyclosporine A (CsA). The target CsA level ranges from 200 to 250 ng/ml.

Address correspondence and reprint requests to Toru Ikegami, MD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan and Fax: +81-92-642-5482.

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Abbreviations

ABO-incompatible (ABOi), acute liver failure (ALF), autoimmune hepatitis (AIH), antibody-mediated rejection (AMR), cyclosporine A (CsA), graft volume (GV), high-flow continuous hemodiafiltration (HF-CHDF), intravenous immunoglobulin (IVIG), living donor liver transplantation (LDLT), mycophenolate mofetil (MMF), model for end stage liver disease (MELD), plasma exchange (PE), standard liver volume (SLV), tacrolimus (Tac)

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autoimmune hepatitis (AIH), graft volume (GV), high-flow continuous hemodiafiltration (HF-CHDF), intravenous immunoglobulin (IVIG), living donor liver transplantation (LDLT), model for end stage liver disease (MELD), standard liver volume (SLV)

### Table 1. Patient demographics and survival data

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Gender</th>
<th>Etiology</th>
<th>MELD score</th>
<th>ABO</th>
<th>Age/Gender</th>
<th>ABO</th>
<th>Relationship</th>
<th>Graft type</th>
<th>GV (g)</th>
<th>GV/SLV (%)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>63 F</td>
<td>AIH</td>
<td>15</td>
<td>O</td>
<td>32 M</td>
<td>A</td>
<td>Son</td>
<td>Left</td>
<td>650</td>
<td>66.1</td>
<td>Dead&lt; 1 month</td>
</tr>
<tr>
<td>#2</td>
<td>21 F</td>
<td>Unknown</td>
<td>19</td>
<td>B</td>
<td>46 M</td>
<td>AB</td>
<td>Mother</td>
<td>Right</td>
<td>520</td>
<td>50.3</td>
<td>Alive 9.1 years</td>
</tr>
<tr>
<td>#3</td>
<td>20 F</td>
<td>Unknown</td>
<td>17</td>
<td>O</td>
<td>54 M</td>
<td>A</td>
<td>Father</td>
<td>Right</td>
<td>600</td>
<td>48.7</td>
<td>Alive 7.8 years</td>
</tr>
<tr>
<td>#4</td>
<td>68 F</td>
<td>AIH</td>
<td>27</td>
<td>A</td>
<td>36 M</td>
<td>AB</td>
<td>Son</td>
<td>Left</td>
<td>499</td>
<td>41.6</td>
<td>Alive 1.0 year</td>
</tr>
<tr>
<td>#5</td>
<td>51 F</td>
<td>AIH</td>
<td>39</td>
<td>O</td>
<td>25 M</td>
<td>A</td>
<td>Son</td>
<td>Left</td>
<td>301</td>
<td>25.1</td>
<td>Alive 10 months</td>
</tr>
</tbody>
</table>

Table 2. Immunomodulation protocols in ABOi-LDLT

<table>
<thead>
<tr>
<th>No.</th>
<th>Local infusion</th>
<th>Rituximab (Pre-LDLT day)</th>
<th>HF-CHDF (days)</th>
<th>Splenectomy</th>
<th>Isogglutinin titer before LDLT</th>
<th>Plasma exchange (Pre- Post-LDLT)</th>
<th>Basic immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Yes (Portal)</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>128 &gt; 32</td>
<td>x2, x5</td>
</tr>
<tr>
<td>#2</td>
<td>Yes (Artery)</td>
<td>Yes (-3)</td>
<td>-</td>
<td>Yes</td>
<td>64 &gt; 2</td>
<td>x2, x5</td>
<td>Tac, MMF, steroid</td>
</tr>
<tr>
<td>#3</td>
<td>-</td>
<td>Yes (-3)</td>
<td>-</td>
<td>Yes</td>
<td>2048 &gt; 64</td>
<td>x6, x5</td>
<td>Tac, MMF, steroid</td>
</tr>
<tr>
<td>#4</td>
<td>-</td>
<td>Yes (-14)</td>
<td>-</td>
<td>Yes</td>
<td>32 &gt; 32</td>
<td>x19, -</td>
<td>CsA, MMF, steroid</td>
</tr>
<tr>
<td>#5</td>
<td>-</td>
<td>Yes (-15)</td>
<td>Yes (11)</td>
<td>Yes</td>
<td>512 &gt; 128</td>
<td>x15, -</td>
<td>Tac MMF, steroid</td>
</tr>
</tbody>
</table>

ABO-incompatible (ABOi), cyclosporine A (CsA), high-flow continuous hemodiafiltration (HF-CHDF), living donor liver transplantation (LDLT), mycophenolate mofetil (MMF), tacrolimus (Tac)

ng/ml for the first post-LDLT month and was titrated down to 100 to 150 ng/ml for the next few months. A gram of methylprednisolone is given after reperfusion, and tapered from 200 mg to 40 mg over 10 days, then switched to 20 mg of oral Prednisolone and tapered off in 6 months after the LDLT.

Plasma exchange (PE) was performed to lower the isoagglutinin titer≤ 64-128. Splenectomy was performed during LDLT.

### Local infusion

Local infusion via the portal vein or hepatic artery was used for between 2001 and 2006 (Table 2). A 16 G double lumen catheter was introduced from the umbilical vein or the mesenteric vein for portal vein or gastricoduodenal artery for hepatic artery. Protease inhibitor (nafamostat mesilate, 200 mg/day), Prostaglandin E1 (500 mcg/day) and methylprednisolone (50 mg/day) were given for 14 days after LDLT.

### Rituximab

Rituximab (500 mg/body) was given has been administered since the Case #2 in 2005. As soon as the indication of the recipient with ALF was confirmed and the donor evaluation including volumetry and hematological/serological tests were completed, rituximab was administered. PE was held at least 8 hours after administration of rituximab and the number of CD-20 positive lymphocytes were evaluated.

### High-flow continuous hemodiafiltration (HF-CHDF)

HF-CHDF was performed as continuous venovenous hemodiafiltration to treat patients with marked comorbidities and general hemodynamic instability. Vascular access was created in the internal jugular vein or the femoral vein, using a 12-Fr flexible triple-lumen catheter (Blood access catheterTM, Arrow International Inc., Reading, PA, USA). A PMMA membrane hemofilter (Hemofeel CHTM, Toray Medical Co. Ltd., Tokyo, Japan) was placed in the circuit. Nafamostat mesilate (FuthanTM, Torii Pharmaceutical Co. Ltd., Tokyo, Japan) was used as anticoagulant, with the dose adjusted to maintain an activated coagulation time of 150-200 seconds. The operating conditions were set as follows: blood flow rate, 150-200 ml/min; dialysate flow rate, 8-20 L/hr; and filtration rate, 1.0-2.0 L/hr. The hemodiafiltration system was continuously monitored with a personal bedside console (JUN-500TM, Ube Medical Co. Ltd., Tokyo, Japan).

### Values

The values are expressed as the mean± standard deviation.

### RESULTS

#### Recipient and donor data

The five recipients who received ABOi-LDLT for ALF included all females, and the mean age was 44.6±19.3 years. The etiologies for ALF included autoimmune hepatitis in three and unknown cause. The mean model for end-stage liver disease score was 23.4±7.7.

The donors included four males and one female, and the mean age, graft volume and graft volume/standard liver volume were, 38.6±9.1 years, 514±91 g, and 46.4±10.4%, respectively (Table 1).

### Immunomodulation for ABOi-LDLT

The desensitization protocol for ABOi barrier included Case #1; local infusion (portal vein)+ plasma exchange (PE), Case #2; local infusion (hepatic artery)+rituximab+PE, Case #3 and #4; rituximab+PE, and Case #5; rituximab+PE under high-flow continuous hemodiafiltration.

When Case #1 was performed, rituximab was not available, and therefore local infusion of steroids, protease inhibitor and prostaglandin, under the control of isoagglutinin titer by PE was performed. Although isoagglutinin titer was controlled without applying PE after LDLT, the patient started to have diffuse thrombosis in the intrahepatic portal system 2 weeks after LDLT, resulting in graft necrosis and death. Although the definite reason for the diffuse portal thrombosis is unclear, we speculate that abrupt discontinuation of intra-portal protease inhibitor and prostaglandin might have caused increased coagulation activity in the portal system.
Case #2 received rituximab 3 days before LDLT and also had local infusión via the hepatic artery. She underwent re-laparotomy two times after LDLT for intraabdominal bleeding and hepatic artery dissection at the catheter tip. She also had AMR on day 7 and were treated by PEs. Since the initial two cases we abandoned local infusión treatment for its catheter associated complications.

Thus, the Case #3 received rituximab without having local infusión despite her pre-transplant isoagglutinin titer was very high (x2048). Although she received PEs after LDLT, she had AMR on day 4. Her AMR was successfully treated by two session of high-dose IVIG on day 5 and 10.

Since then, we changed our policy in ABOi-LDLT again, and planned to put rituximab 2 weeks before LDLT and apply HF-CHDF to keep a patient away from brain death due to hepatic coma. Because the Case #4 did not have rapid progressive encephalopathy, she did not received HF-CHDF and underwent scheduled LDLT 2 weeks after having rituximab. On the other hand, Case #5 started to have grade II encephalopathy when she received rituximab, and therefore she was on HF-CHDF for 11 days before LDLT. The last two cases had fairly good post-transplant course.

**Graft outcomes**

The isoagglutinin titer after LDLT showed rebound elevation in the Case #2 and #3, both of which received rituximab within a week before LDLT, with deteriorating liver function tests indicating AMR. In both cases, CD-20 positive lymphocyte number was zero after LDLT despite their clinical AMR. Nevertheless, their AMR episodes were successfully treated by PE with or without IVIG.

Graft was lost only in the Case #1, and therefore graft survival rate was 80% with good graft function over 3.8±3.7 years.

**DISCUSSION**

Because there has been a very limited chance to perform liver transplantation from deceased donors in Japan, the use of ABOi donors are often required in LDLT (3-5). Thus, various methods have been implemented to allow these procedures, including local infusion (9). The theoretical basis of local administration of protease inhibitors, prostaglandin, and steroids is that the pathological findings of the failed ABOi liver graft show the features of hepatic disseminated intravascular coagulation (9). Although local infusion is a theoretically reasonable treatment of choice, there are problems associated with its application via the portal vein or hepatic artery includes catheter-related complications, and possible re-laparotomy for the removal of the catheters (10-12).

Rituximab, an anti-CD20 antibody, is a monoclonal antibody that specifically targets the CD20 surface antigen expressed on B lymphocytes, thus resulting in cell lyses. In the current series, the Case #3 and #4 were given Rituximab just 3 days before LDLT, and had rebound elevation of isoagglutinin titer with clinical AMR. Usui et al. (4) reported on its use as long as 3 weeks before the LDLT with successful outcomes. Egawa et al. (12) has reported that administration of rituximab earlier than 7 days before LDLT significantly depleted B- and memory B-lymphocytes. However in treating the patients with ALF, LDLT needs to be timely performed and high-dose IVIG could be applied as a prophylaxis for AMR (Figure 1).

In conclusion, refinements and revisions in ABOi-LDLT were performed over fourteen years of experiences, and currently rituximab-based ABOi-LDLT under HF-CHDF is our choice for treating deteriorating patients with ALF.

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**AUTHOR CONTRIBUTIONS**

Mitsuhiro Yasuda : drafting of manuscript
Toru Ikegami : study concept and design
Huanlin Wang : data collection
Yuki Bekki : data analysis
Daisuke Imai : data collection
Shinji Itoh : data collection
Noritumi Harimoto : data collection
Tomoharu Yoshizumi : data collection
Ken Shirabe : study design and critical revision of the manuscript
Yoshikiko Maehara : final approval of the manuscript

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