ABO-Incompatible Living Donor Liver Transplantation: New Insights into Clinical Relevance

Naoki Kawagishi and Susumu Satomi

Short-term outcome of the ABO-incompatible liver transplantation has been improved dramatically due to novel immunosuppressive protocols and apheresis. This review will discuss current understanding of the clinical relevance of ABO-incompatible liver transplantation including long-term outcome mainly from the Japanese experience.

Keywords: ABO-incompatible, Apheresis, Infusion therapy, Living donor liver transplantation, Rituximab.

In most countries where deceased donors are the main source of grafts, the recipients are selected based on ABO histo-blood group type. Therefore, ABO-incompatible (ABO-I) liver transplantation (LT) is carried out only in an emergency, and the results are usually not satisfactory (1, 2). The main reason for a poor result is severe hyperacute rejection due to anti-donor ABO antibodies during the early postoperative period. Once anti-blood type antibodies attach to the blood type antigens existing on the vascular endothelial cells, this causes damage to the endothelial cells. This phenomenon is introduced by the production of substances such as cytokines, chemotactic factors, and free radicals, and is accompanied by platelet and complement activation, thrombus formation, granulocyte and macrophage migration, and phagocytosis by granulocytes and macrophages. Moreover, it was reported that the other complications of ABO-I LT, such as hepatic necrosis and intrahepatic biliary complications, were closely related to a high perioperative anti-A or anti-B Ab titer (3). Thus, most of the efforts to improve the outcome of ABO-I LT have been directed toward the elimination of anti-blood type antibodies. Particularly, the impact of preformed anti-donor ABO antibodies and the strategy to reduce their titers play key roles in the success of this in pediatric ABO-I living donor liver transplantation (LDLT) (4–6). To reduce the preformed anti-donor ABO antibodies, apheresis is mainly performed before transplantation. In addition, splenectomy is performed during the operation to reduce the source of antibodies production. Although these procedures have contributed to the success of transplantation in pediatric patients, conventional apheresis and splenectomy had almost no effectiveness in adult patients (3). But recent advances on portal vein or hepatic artery infusion therapy have led to great improvement of the outcome of adult ABO-I LDLT (Fig. 1) (4, 7). The target of this therapy is to control the local intravascular coagulation in the graft. Prostaglandin E1, gabexate mesylate, and methylprednisolone are infused through the catheter. Prostaglandin E1 improves hepatic blood flow and microcirculation through its vasodilating effects and inhibits platelet and leukocyte adhesion. Gabexate mesylate is a serine protease inhibitor that inhibits thrombin, Xa, and platelet aggregation. These therapies pushed up the 2-year adult recipient survival rates after ABO-I LDLT in Japan from around 40% to 70% since 2002 (8).

Another new strategy for ABO-I LDLT has been adopted based on the experience with rituximab for kidney transplant recipients (9). Rituximab is a monoclonal chimeric human-murine anti-CD20 antibody that depletes the B cells by complement-dependent cytotoxicity, drug-induced apoptotic death, and antibody-dependent cellular cytotoxicity. Rituximab has been approved for the treatment of relapsed or refractory B-cell non-Hodgkin’s lymphoma. We had good results in children without using rituximab before 2000, but we changed the strategy for ABO-I cases after we experienced a fatal case of humoral rejection in 2000. Namely, we first reported the use of rituximab in LDLT recipients in 2002 (10), successfully treating rejection episodes in a patient who had not responded to other forms of treatment. Some other reports also supported the effectiveness of the rituximab for the antibody-mediated rejection (11, 12). Recently, Egawa et al. (12) reported the timing of the rituximab administration in ABO-I LDLT recipients, and this report concluded that early prophylaxis with rituximab depletes B cells, including memory B cells, in the spleen and was associated with a trend toward lower antibody-mediated rejection rates. And currently, in the living donor kidney transplantation in...
Complications related to antibody-mediated rejection (AMR) in LDLT in Japan is around 80% (green line: n = 64, red line: n = 78, purple line: n = 15) (Japan Study Group for ABO Blood Type Incompatible Transplantation 2007).

Another strategy for the ABO-I LDLT is intravenous immunoglobulin therapy. Data on the introduction of rituximab and infusion therapy, which have yielded excellent results after ABO-incompatible LDLT, are limited. Particularly, in some recipients peripheral CD19 positive B cells disappeared completely for more than 1 year after a single dose of rituximab of 375 mg/m². This phenomenon was expected to proceed without severe complications if peri-operative complications such as antibody-mediated rejection are overcome.

Although the short-term survival rate improved after the introduction of rituximab and infusion therapy, data on the long-term outcome and adverse effects were scarce (Table 1). Particularly, in some recipients peripheral CD19 positive B cells disappeared completely for more than 1 year after a single dose of rituximab of 375 mg/m². This phenomenon was not seen in patients under treatment for lymphoma. Portal vein or hepatic artery infusion therapy may lead to intravascular thrombosis or the development of an aneurysm. Some other institutions in Japan have experienced catheter related complications demonstrating that this is a genuine risk of this treatment.

The long-term outcomes of pediatric ABO-I LDLT are not significantly different from ABO-compatible cases (8). Similarly, the survival of the living donor kidney series of ABO-incompatible recipients including adults in Japan showed no differences compared with ABO-compatible transplants. This showed that the influence of blood type-related immunological factors was almost eliminated once accommodation was established in the living donor kidney transplantation. Most of the cases, the antibody titers became low in the long-survived recipients. We hope that the same thing will happen to the adult recipients of LDLT, but it takes more time to show the result. And it will be possible that these evolutions of immunosuppressive protocols in ABO-I LDLT adapt for other organ transplantations in the future (Table 2).

In conclusion, rituximab and infusion therapy have been used in ABO-incompatible LDLT in Japan, our results indicate that rituximab and infusion therapy will become a new strategy for ABO-incompatible liver transplantation even in other countries. Like those recipients who were subjected to ABO-I LDLT during their childhood without receiving rituximab or infusion therapy, they are spending their lives like ABO-compatible or -identical recipients, many adults who received rituximab or infusion therapy are also spending normal daily lives. Finally, in terms of long-term outcome, survival after ABO-incompatible LDLT can be expected to proceed without severe complications if peri-operative complications such as antibody-mediated rejection are overcome.

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TABLE 1. Current outcome of ABO-I LDLT in Japan and complications related to antibody-mediated rejection (AMR)

<table>
<thead>
<tr>
<th>No. ABO-I LDLT</th>
<th>Complications related to AMR</th>
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<tbody>
<tr>
<td>(1991–2007 March)</td>
<td>Hepatic necrosis</td>
</tr>
<tr>
<td>n = 326</td>
<td>Intrahepatic biliary complications</td>
</tr>
<tr>
<td>Outcome (alive)</td>
<td>n = 226</td>
</tr>
</tbody>
</table>

TABLE 2. Improvement of the immunosuppressive advance in LDLT in Japan

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>1991</td>
<td>First case of ABO-I LDLT in Japan</td>
</tr>
<tr>
<td>1998</td>
<td>Portal vein infusion therapy</td>
</tr>
<tr>
<td>2001</td>
<td>Hepatic artery infusion therapy</td>
</tr>
<tr>
<td>2002</td>
<td>Rituximab</td>
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</table>

FIGURE 1. Patient survival curve on ABO-I LDLT patients 16-year-old or older. The introduction of rituximab and infusion therapy has yielded excellent results after ABO-incompatible LDLT even in adults. Infusion therapy was introduced since 1998, and rituximab was introduced since 2002. Current 2-year patient survival in ABO-compatible LDLT in Japan is around 80% (green line: n = 64, red line: n = 78, purple line: n = 15) (Japan Study Group for ABO Blood Type Incompatible Transplantation 2007).


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