Living Donor Liver Transplantation Across The ABO Blood Type Barrier

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Liver transplantation across ABO blood groups

Robert D. Gordon, M.D., Shunzaburo Iwatsuki, M.D., Carlos O. Esquivel, M.D., Ph.D., Andreas Tzakis, M.D., Satoru Todo, M.D., and Thomas E. Starzl, M.D., Ph.D., Pittsburgh, Pa.

Six hundred seventy-one first, second, and third orthotopic liver allografts in 520 patients were reviewed to determine the effect of donor-recipient mismatches or incompatibilities for the ABO blood groups on graft survival. A significant advantage for ABO donor-recipient identity was found, especially in adults and for first grafts. However, a surprisingly large number of ABO incompatible grafts were successful. We recommend that nonidentical or incompatible grafts be limited to patients such as small children for whom the supply of available donors is severely limited or for patients in urgent need of transplantation or retransplantation.

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pa.

Surgery 1986;100:342-348
**Blood Type Incompatible Liver Transplantation**

- Cadaveric Liver Transplantation
  
  **CONTRAINDICATION**
  or only in an emergent situation

- Living Donor Liver Transplantation
  
  **Donor selection is highly limited.**
  → When the only available graft is ABO incompatible
Annual number of LDLT in Kyoto

![Graph showing annual number of LDLT in Kyoto with bars for years 1990 to 2004, with shaded sections indicating identical or compatible and unshaded sections indicating incompatible.]
Cause of Death in ABO-I Liver Transplantation

Infection

Hepatic necrosis

Intrahepatic biliary complication

Over immunosuppression

Humoral rejection
Day 26

Onset: 1-3 weeks
Fever
Increase in antibody titers
Decrease in platelet counts
Increase in transaminase levels

Rapid development in the whole graft
Hepatic failure
Hepatic Necrosis

AB(+)→O(+), PBC

<table>
<thead>
<tr>
<th>PE</th>
<th>antiA IgG</th>
<th>256</th>
<th>8</th>
<th>16</th>
<th>128</th>
<th>512</th>
<th>512</th>
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<td>32</td>
<td>32</td>
<td>8</td>
<td>4</td>
<td>2</td>
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</tbody>
</table>

euphoria  
CT  
intubation

AST
ALT
PLT
Intrahepatic Bile Duct Lesion

Clinical picture

Clinical onset:
1-3 months after LTx

Sclerosis or mixture of stenosis and dilatation, similar to PSC

Repeated cholangitis leading to graft failure
LONG TERM FOLLOW-UP OF ABO-INCOMPATIBLE LIVING-DONOR LIVER TRANSPLANTATION: RELATION BETWEEN OUTCOME AND AGE OF RECIPIENTS

Egawa et al.
Transplantation 2004;77:403

- June 1990 - February 2000
- 66 patients (13% in 523 patients)
- 10 months to 55 years old (median 2 years)
Cases

Incompatible

Identical

compatible

13%

1~8 y.o.

8~16 y.o.

<1 y.o.

ICU

Hosp.

At Home

At Home

Hosp.

Patients

13%

Transplantation Egawa et al
Patients and complication

Older children
IHBC $\rightarrow$
hepatic necrosis $\rightarrow$
Adult

Strategy

Base: tacrolimus & steroid plasma pheresis, blood exchange

OKT3 (#25 – #56)
splenectomy (#111 –)
AZA (#175–)
weekly pulse (#266 –)
cyclophosphamide (#306 –)

Until 2000

Transplantation Egawa et al
Compatibility and Survival

Transplantation Egawa et al
ABO Compatibility and Age
Survival after LDLT

Identical & Compatible

Incompatible

Transplantation Egawa et al
## Age and complications

<table>
<thead>
<tr>
<th>Age</th>
<th>Patients group</th>
<th>Necrosis</th>
<th>IHBC</th>
<th>Normal</th>
<th>Other</th>
<th>Total</th>
<th>death</th>
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<td>&lt;1 y.o.</td>
<td>0</td>
<td>0</td>
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<td>5</td>
<td>1</td>
<td></td>
<td>11</td>
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<tr>
<td>16y.o. &lt;</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4</td>
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<td>9</td>
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<tr>
<td>Total</td>
<td>5</td>
<td>12</td>
<td>32</td>
<td>17</td>
<td></td>
<td>66</td>
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</table>

*p<0.01: chi-square test*

Two patients surviving shorter than 1 week were not included in this analysis.
Change of antibody titer

3 – 7 days after transplantation

Uneventful course
or
Humoral rejection

Antibody titer

Plasma-pheresis

Long term Follow-up

Transplantation Egawa et al
Correlation between pre & post LTx - IgM, IgG peaks

- Pre-LTx IgM peak
  - Post-LTx IgM peak: ns

- Pre-LTx IgG peak
  - Post-LTx IgG peak: significant
  - Pre-LTx IgM peak: ns

Post-operative change of IgM titer in recipient age groups

IgM titer (times)

- □ <1
- ○ > 1 to <8
- ■ > 8 to <16
- ● > 16

Transplantation Egawa et al
Post-operative change of IgG titer in recipient age groups

IgG titer (times)

Post-operative peak at LTx

Preoperative peak

Last follow-up

Transplantation Egawa et al
Preoperative peak IgM titer and postoperative course in recipient age groups

- hepatic necrosis
- IHBC
- uneventful
- other death

Transplantation Egawa et al
Preoperative peak IgG titer and postoperative course in recipient age groups

- Hepatic necrosis
- IHBC
- Uneventful
- Other death

Preoperative peak IgG titer of IgG (times)

Age group:
- <1
- 1 to <8
- 8 to <16
- > 16

Transplantation Egawa et al
Postoperative peak IgM titer and postoperative course in recipient age groups

Postoperative peak IgM titer of IgM (times)

- hepatic necrosis
- IHBC
- uneventful
- other death

Transplantation Egawa et al
Postoperative peak IgG titer and postoperative course in recipient age groups

- hepatic necrosis
- IHBC
- uneventful
- other death

Transplantation Egawa et al
Pathology of ABO-related rejection

Natural antibody against donor blood-type

Binding to the antigen on graft endothelium

Complement activation

Vasospasms

Platelet aggregation

Local DIC

Compliance with the antigen on graft endothelium

Increase of antibody titers

Decrease of platelet

Disturbance of microcirculation of terminal arteries for biliary tree

Hepatic Necrosis

Biliary Lesion

Crisis in total graft circulation

First week

mild - moderate

severe

mild - moderate
Periportal Edema and Necrosis (PEN)

Haga et al
Liver Transplantation 2004;6:16-27
periportal edema and necrosis (PEN)

thrombus in the arteriole
PEN with cellular rejection

lymphocytic infiltration, periportal hemorrhage
centrilobular endothelialitis, without necrosis
C4d – IgG/IgM in a hepatic necrosis case
Tactics

- Decrease antibody titer
- Decrease antigen-antibody-compliment reaction
- Decrease endothelium injury
- Decrease thrombus
- Improve microcirculation
Two successful cases with intraportal infusion therapy for ABO incompatible liver transplantation
PGE1, Steroids, and Gabexate Mesilate
Portal Infusion Catheter
# Portal Infusion Protocol

<table>
<thead>
<tr>
<th>Pre</th>
<th>Plasma Exchange (anti A IgM, anti B IgM &lt; 8)</th>
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<tr>
<td>Ope.</td>
<td>LTx &amp; Splenectomy</td>
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<td>Post</td>
<td>Portal Infusion</td>
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<tr>
<td></td>
<td>Methylprednisolone 125mg/day, ~1w</td>
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<td></td>
<td>50mg/day, ~2w</td>
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<tr>
<td></td>
<td>Prostaglandine E1 0.01 γ, ~3w</td>
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<tr>
<td></td>
<td>Gabexate Mesilate 1000mg/day, ~3w</td>
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<td></td>
<td>General Immunosuppression</td>
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<tr>
<td></td>
<td>Cyclophosphamide 2mg/kg/day, ~2w(iv), ~4w(oral)</td>
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<tr>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
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<tr>
<td>Case</td>
<td>Original Disease</td>
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<tr>
<td>------</td>
<td>------------------</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>610</td>
<td>HCV,LC</td>
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<tr>
<td>639</td>
<td>HBV,LC,HCC</td>
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<tr>
<td>98</td>
<td>BA,ReLTx</td>
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<tr>
<td>651</td>
<td>AIH</td>
</tr>
<tr>
<td>666</td>
<td>PSC</td>
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<tr>
<td>675</td>
<td>HCV,LC,HCC</td>
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<td>HBV,LC,HCC</td>
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<td>693</td>
<td>HCV,LC</td>
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<tr>
<td>698</td>
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<tr>
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<td>PBC</td>
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<td>BA</td>
</tr>
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<td>779</td>
<td>BA</td>
</tr>
<tr>
<td>239</td>
<td>ReLTx</td>
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<tr>
<td>848</td>
<td>HCV,LC,HCC</td>
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</table>
Patient Survival of adult ABO-I LDLT

Actuarial Patient Survival Rate

PV infusion

No infusion

days
Prostaglandin E1

**Vasodilatation**

**Inhibition of platelet aggregation**

**Inhibition of proinflammatory cytokine production**
Prostaglandin E1 reduces myocardial reperfusion injury by inhibiting proinflammatory cytokines production during cardiac surgery.
The modulatory effects of prostaglandin-E on cytokine production by human peripheral blood mononuclear cells are independent of the prostaglandin subtype.

**Angiogenesis**
Clinical and experimental evidence of prostaglandin E1-induced angiogenesis in the myocardium of patients with ischemic heart disease.

**Immune modulation**
A new view of prostaglandin E regulation of the immune response.
Effects of prostaglandin E1 on the production of IgM and IgG class anti-dsDNA antibodies in NZB/W F1 mice.

2003 Kyoto University Hospital
PGE1

Inhibition of cytokines
Inhibition of aggregation
Protect endothelium
Vasodilatation

Kupffer cell

Compliment

IL-6

TNF-α

IL-1β

Platelets

Endothelium

Vascular smooth muscle cell

Thrombus

B cell

Inhibition of cytokines
Inhibition of aggregation

Vasodilatation

Steroid
Hepatic necrosis under PV infusion

Case 707  AB (+) to O(+), PBC

preope.

antiA IgG  256
antiA IgM  64
anti B IgG  2048
anti B IgM  32

9POD
Encephalopathy
gradeII

antiA IgG  512
IgM  512
anti B IgG  64
IgM  32
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<tr>
<th>ABO-related rejection</th>
<th>Vasculopathy</th>
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<tr>
<td><strong>Intimal hypertrophy of hepatic artery</strong></td>
<td><strong>Inflammation of hepatic artery</strong></td>
</tr>
<tr>
<td>Hepatic necrosis (explant)</td>
<td>Intra-hepatic Biliary Complication (explant)</td>
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</table>
Significance of HA circulation in ABO-I related complication

Liver necrosis

Bile duct injury

Liver necrosis
Sclerosing hepatic artery after ABO-I liver transplantation
Portal infusion therapy is not enough for controlling ABO-related rejection.

Severe attack of hepatic necrosis in one case despite the use of portal infusion therapy

Hepatic arterial infusion therapy is more directly effective in preventing the arteriole injury by ABO incompatibility!
## PV + HA Infusion Protocol

### Pre
- Plasma Exchange (anti A IgM, anti B IgM < 8)

### Ope.
- LTx & Splenectomy

### Post
- Portal Infusion
  - Methylprednisolone: 125mg/day, ~1w, 50mg/day, ~2w
  - Prostaglandine E1: 0.01 γ, ~3w
  - Gabexate Mesilate: 1000mg/day, ~3w

### General Immunosuppression
- Cyclophosphamide: 2mg/kg/day, ~2w(iv), ~4w(oral)
- Tacrolimus
- Methylprednisolone

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**Kyoto protocol**

---

2003 Kyoto University Hospital
Placement of Hepatic Artery Catheter

HA catheter

LHA

RHA

PHA

GRAFT
Placement of Hepatic Artery Catheter

(A)

(B)

(C)

(D)
<table>
<thead>
<tr>
<th>Case</th>
<th>Original Disease</th>
<th>Blood Type</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Hepatic Necrosis</th>
<th>Biliary Lesion</th>
<th>Infection</th>
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<tr>
<td>728</td>
<td>HCV, LC, HCC</td>
<td>A</td>
<td>dead</td>
<td>(44) days</td>
<td>(+) moderate</td>
<td>(-)</td>
<td>Sepsis, CMV</td>
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<tr>
<td>731</td>
<td>HCV, LC</td>
<td>A</td>
<td>alive</td>
<td>519</td>
<td>(-)</td>
<td>(-)</td>
<td>CMV</td>
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<tr>
<td>738</td>
<td>BA, HCV, HCC</td>
<td>A B</td>
<td>alive</td>
<td>500</td>
<td>(-)</td>
<td>(-)</td>
<td></td>
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<tr>
<td>797</td>
<td>HCV, LC, HCC</td>
<td>A O</td>
<td>alive</td>
<td>281</td>
<td>(-)</td>
<td>(-)</td>
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<tr>
<td>134</td>
<td>ReLTx</td>
<td>AB A</td>
<td>alive</td>
<td>272</td>
<td>(+) mild</td>
<td>(-)</td>
<td>CMV</td>
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<tr>
<td>799</td>
<td>PBC</td>
<td>AB B</td>
<td>alive</td>
<td>269</td>
<td>(-)</td>
<td>(-)</td>
<td>CMV</td>
</tr>
<tr>
<td>817</td>
<td>PBC</td>
<td>B O</td>
<td>alive</td>
<td>199</td>
<td>(+) HAT</td>
<td>(-)</td>
<td>Sepsis, CMV</td>
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<tr>
<td>820</td>
<td>PBC</td>
<td>A O</td>
<td>alive</td>
<td>185</td>
<td>(+) mild</td>
<td>(-)</td>
<td>CMV</td>
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<tr>
<td>836</td>
<td>HCC, LC, HCV</td>
<td>A O</td>
<td>alive</td>
<td>122</td>
<td>(-)</td>
<td>(-)</td>
<td>CMV</td>
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</tbody>
</table>

PV+HA Infusion Protocol

- PGE1, steroids (Hepatic artery infusion)
- Gabexate Mesilate (Portal infusion)

#728, 731, 738, 797, 134, 799, 817

PGE1, steroids (Hepatic artery infusion), No portal infusion

#820, 836:
Patient Survival of adult ABO-I LDLT

Actuarial Patient Survival Rate

- PV+HA Infusion
- Portal Infusion
- Before Portal Infusion
Problems to be solved

Over-immunosuppression

High incidence of CMV infection

14/17 82.4% portal infusion
7/9 77.8% hepatic artery infusion

- General immunosuppression should be weakened?
- Tailored for the risk?
Catheter related complication

Hepatic Arterial Thrombosis

Hepatic arterial & portal catheter infusion therapy: 1/9 (11.1%)

portal infusion therapy: 1/17
identical/compatible transplantation: 4/350
using right lobe

- Catheter-related?:
  - material
  - strong anticoagulant treatments
  - position of the catheter tip

- Endothelial injury associated with ABO incompatibility?
Catheter related complication

Portal thrombosis

9 patients developed portal thrombosis in 26 patients with portal infusion.
Portal infusion therapy: 4/17
Hepatic arterial & portal infusion therapy: 5/9

Total: 35%
ABO Incompatible LDLT

Portal catheter

spleenectomy

thrombocytosis

lack of splenic venous return

Portal thrombosis

Next strategy

Hepatic arterial infusion therapy
without portal catheter
without splenectomy
Patient Survival of adult ABO-I LDLT

- HA infusion without splenectomy
  - PVT decrease from 35% to 8%

- PV+HA infusion
- PV infusion
- before infusion era

(HCC rec)
Effect on splenectomy on Post-transplant peak titer

Anti-A or B IgM

With splenectomy

Without splenectomy

Antibody titer increased!

Anti-A or B IgG

P=0.037

P=0.036

n=10

n=17

n=9

n=13
Tactics: decrease Ab titer

- Splenectomy
  - Possible permanent immuno-defficiecy
  - Cause of portal thrombus

B cell deletion by Rituximab instead splenectomy
Correlation between Pre-LTx IgG peak & Post-LTx IgG peak

Incompatible related complication

- Adult cases
- Hepatic necrosis
- IHBC
- Uneventful
Change of lymphocyte population

Adults (n=15)
IgG peak & CD20 peak after ABO-I LTx with HA infusion

IgG titer

CD20 (%)
IgM peak & CD20 peak after ABO-I LTx with HA infusion

- Hepatic necrosis

IgM titer:
- 2048
- 512
- 128
- 32
- 8

CD20 (%):
- 20
- 30
- 40
- 50
Change of CD20 and antibody titer

-1mo  LTx  1mo  2mo  3mo

Antibody titer

CD20(%)  50

50  40

30

20

10

128

32

8

512

2048

12yo F re-Tx for CR
HA infusion without splenectomy

IgG

IgM
Day 26 (2004.1.23) Cholangitis-like ductular reaction with cholestasis and centrilobular necrosis (late phase of humoral rejection)
Application of Rituximab

1. Rescue therapy for elevated antibody after LTx (n=4)

2. Prophylaxis before LTx (n=6)
All cases: HA infusion without splenectomy

**Post-LTx peak IgM**

- **Ritx (-)**
- Rescue
- Prophylaxis

**Post-LTx peak IgG**

- **Ritx (-)**
- Rescue
- Prophylaxis
### 6 cases with Rituximab Prophylaxis

<table>
<thead>
<tr>
<th>Case</th>
<th>name</th>
<th>sex</th>
<th>age</th>
<th>day of Ritux</th>
<th>pre-ope IgM</th>
<th>pre-ope IgG</th>
<th>post-ope IgM</th>
<th>post-ope IgG</th>
<th>PEN</th>
<th>result</th>
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<td>1</td>
<td>S.M.</td>
<td>f</td>
<td>29</td>
<td>−2</td>
<td>128</td>
<td>256</td>
<td>512</td>
<td>256</td>
<td>y</td>
<td>D(peritonitis)</td>
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<tr>
<td>2</td>
<td>I.Y.</td>
<td>f</td>
<td>65</td>
<td>−6</td>
<td>64</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>n</td>
<td>alive</td>
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<tr>
<td>3</td>
<td>M.Y.</td>
<td>f</td>
<td>58</td>
<td>−15</td>
<td>128</td>
<td>2048</td>
<td>64</td>
<td>128</td>
<td>n</td>
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<tr>
<td>4</td>
<td>N.T.</td>
<td>f</td>
<td>38</td>
<td>−3</td>
<td>512</td>
<td>1024</td>
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<td>128</td>
<td>y</td>
<td>D(pneumonia)</td>
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<td>H.K.</td>
<td>m</td>
<td>57</td>
<td>−2</td>
<td>1024</td>
<td>64</td>
<td>128</td>
<td>32</td>
<td>n</td>
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<td>6</td>
<td>S.H.</td>
<td>f</td>
<td>61</td>
<td>−4</td>
<td>64</td>
<td>256</td>
<td>1</td>
<td>2</td>
<td>n</td>
<td>alive</td>
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## Results

<table>
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<tr>
<th></th>
<th>HA infusion Rituximab (-)</th>
<th>HA infusion Rituximab rescue</th>
<th>HA infusion Rituximab prophylaxis</th>
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<tbody>
<tr>
<td>Pathological humoral rejection</td>
<td>3 / 13</td>
<td>2 / 4</td>
<td>2 / 6</td>
</tr>
<tr>
<td>Total necrosis</td>
<td>0 / 13</td>
<td>2 / 4</td>
<td>0 / 6</td>
</tr>
<tr>
<td>Intrahepatic biliary complication</td>
<td>0 / 13</td>
<td>0 / 4</td>
<td>0 / 6</td>
</tr>
<tr>
<td>death</td>
<td>2 / 13</td>
<td>2 / 4</td>
<td>2 / 6</td>
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<tr>
<td>pneumonia</td>
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</table>
Strategy for the Blood Type Barrier in Kyoto

Base: tacrolimus & steroid plasma pheresis, blood exchange

Infants

Older children

Adults

OKT3 (1991)

spleenectomy (1994)

AZA (1995)

weekly pulse (1997)

cyclophosphamide (1997)

Portal infusion (2000)

HA+PV infusion (2001)

HA infusion (2003)

Keep spleen (2004)

Rituximab (2004)
Japanense Registry of ABO incompatible Liver Transplantation 2004

- 194 patients in 31 centers
- All living donor liver transplantation
ABO-I LDLT in Japan

(Japanense Registry 2004)

( until March/31)
Japanese Registry 2004

Recipient

Gender
- female
- male

Preoperative status
- ICU
- At home
- hospitalized
- unknown
Ground father

Brother in law

spouse

siblings

child

parent

Donor

Japanense Registry 2004
Indications

- Biliary atresia: 85
- HCC: 16
- LC due to viral hepatitis: 10
- FHF: 14
- Re-Tx: 14
- PBC: 11
- PSC: 4
- Metabolic: 11
- AIH: 3
- others: 11
- unknown: 4
# Infusion therapy

<table>
<thead>
<tr>
<th>Catheter</th>
<th>patient #</th>
<th>Spleen kept</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>PV+HA</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>HA</td>
<td>24</td>
<td>18</td>
</tr>
</tbody>
</table>

Age of children with a HA catheter: 0, 5, 8, 10, 10, 14, 14, 14 y.o.
HA Catheter related Complications

- Bleeding
- HAT
- Dislocation
- Bile anastomosis injury by pulling HA catheter
Humoral rejections

- Intrahepatic biliary complication: 17
  - Death: 7
  - Infection: 5
  - Esophageal varices: 1
  - Pulmonary hypertension: 1

- Hepatic necrosis: 23
  - Death: 17
  - Graft failure: 16
  - Infection: 1

Patients began to survive necrosis in “infusion era”.

Japanese Registry 2004
Blood Type Combination and Mortality

Japanese Registry 2004
Blood Type Combination and Mortality

Age ≥ 8 y.o.

Japanense Registry 2004
Causes of Death

- Infection 23
- Hepatic necrosis 16
- Graft failure 4
- Vascular Complication 3
- Gastric ulcer 1
- Esophageal varices 1
- Chronic rejection 1
- Pulmonary hypertension 1
- Recurrence of native disease 1
- Others 7
What is next?

Introducing accommodation by Inactivating blood type antigens by Modulating glycosyltransferase