ABO incompatible kidney transplantation

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When do we face ABO incompatible organ transplant?

Anti-A
Anti-B

Anti-B

A

A

O

No natural (IgM) isoagglutinins
ABO incompatible kidney transplantation has been developed in a large scale in Japan, because the concept of brain death was only accepted there in 2010

- Lack of ABO compatible kidney or liver transplants

Major problem with ABO incompatible organ transplantation:

- Acute vascular / humoral rejection (AMR)
  - Originally prevented by splenectomy at the time of kidney transplantation
  - Since 2000 splenectomy has been replaced by rituximab infusion pretransplant [CD20 (+) cells depletion]
  - In COMBINATION with pretransplant
    - Plasma exchanges or immunoadsorption performed until isoagglutinin titer becomes lower then < 1/8 or < 1/16
  - Independent predictive factors of AMR:
    - IgG isoagglutinin titer at the time of transplantation, i.e. if > 1/32 [OR = 9.52]
    - Pretransplant DSA [OR=5.68]

Very good results (patient/graft) in the long-term
Isoagglutinins

• Ig M isotype (natural antibodies) or IgG isotype (after alloimmunisation)

• Assessment by tube dilution (in-house technique) (Ig M + IgG)
  ➢ Titration : 1; ½; ¼; 1/8; 1/16 or 1; 1/5. 1/10; etc..

• In case of ABO incompatible organ transplantation, if no desensitization is attempted vascular rejection will occur within a few days posttransplantation, and the allograft will be lost
  ➢ Lower down isoagglutinin titer towards 1 by pretransplant plasmapheresis (or immunoadsorption –IA-) + Rituximab (or splenectomy); IVIg are NOT required
  ➢ If isoagglutinin titers remain > 1/16 potential risk of vascular rejection

• It is easier to desensitize when the donor is A2 instead of A1
HOW CAN WE DECREASE ISOAGGLUTININS?

➔ By desensitization
• **Immunosuppressive therapy, i.e.**
  – Rituximab
  – Tacrolimus, MMF, and steroids

• **Apheresis, i.e.**
  – Plasmapheresis
  – Double filtration plasmapheresis
  – Specific immunoabsorption (Glycorex® columns)
  – Semi-specific immunoabsorption (Immunosorba® or Globaffin® columns)
Median changes in anti-A/B IgG titre before ABOi kidney transplantation and during the first two postoperative weeks (n=43) after Immunoadsorption + Rituximab

The area within the broken lines represents the IQR. Light gray arrow represents single-dose anti-CD20 monoclonal antibody (rituximab). Black arrows represent Glycosorb®-ABO IAs and the black diamonds represent the anti-A/B IgG titre in vivo immediately after completed IA. BL, baseline, i.e. at referral; IA, Glycosorb®-ABO IA.

Genberg H. et al. NDT 2011;26(7):2394-2400
Median changes in anti-A/B IgG titre in the long-term following ABOi kidney transplantation (n=41)

The area within the broken lines represents the IQR. (P = not significant).

Genberg H. et al. NDT 2011;26(7):2394-2400
The median anti-donor IgG Isoagglutinin titres significantly decreased after rituximab treatment in the ABOi group ($P = 0.0012$).

Habicht A. et al. NDT 2011;26:4124-4131
DESENSITIZATION PROTOCOLS in the setting of ABOi kidney transplantation
**ABOi kidney transplantation: the Japanese protocol**

**Tac (0.15 mg/kg/d) + MMF 2 gr/d + steroids**

-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6

---

**DFPP:** double filtration plasmapheresis

**ATG or Basiliximab**

Splenectomy or Rituximab

**Isoagglutinins titration**

\[ \leq 1:32 \]

DFPP: double filtration plasmapheresis

ATG: antithymocyte globulins

Ishida et al. AJT 2007;7; 825
Tyden protocol (Sweden)

RTX 375 mg/m²

Tac/Cs/MMF

No Heparin

IAdsorption

IVIg

-30 -10 -6 -5 -3 -2 -1 0 2 5 8 days

pre-KTx : A/B titer:
post KTx : if ↑ A/B titers and/or ↑ creatinine -→ IAdsorption

≤ 1:4
Immunosuppressive regimen in ABO-incompatible living kidney transplantation at TWMU (Japan)

Tac: tacrolimus, MMF: mycofenolate mofetil.

Tac: 0.03mg/kg/day d.i.v. 0.1mg/kg/day
MMF: 2000mg/day 1500mg/day
Steroids: 20mg
Rituximab: 200mg/pt
basiliximab: 20mg
PP: 7 days
ABOi KTx in Toulouse: adapted from Tyden’s protocol (1)

- **Rituximab 375 mg/m²**
  - D-30
- **Prednisone 0.5 mg/kg/d**
  - IA
  - D-20
  - D-10
  - D-6
  - D-5
  - D-2
  - D-1
- **Tacrolimus 0.075 mg/kg x 2/d [8-12 ng/mL]**
  - IA
  - IA
  - IA
  - IA
- **Myfortic 720 mg x 2/d**
  - IA
  - IA
  - IA
  - IA
- **Thymoglobulin 1.25 mg/kg**
  - D1
  - D2
  - D4
  - D6
Or **Basiliximab 20 mg D0 and D4**

≤ 1:4
Posttransplant

**Tacrolimus** [trough levels: 8-12 mg/mL til day 15 then 6-9 ng/mL]

Myfortic 720 mgx 2/d til day 15 then 360 mgx2/d

**Steroids** (1/2 mg/kg at D8 then 20 mg/d til day 15 then tapered to 5 mg/d)

Isoagglutinins titration ($\leq 1/4$)

Then twice/month → M6 then 1x /month

KB

M1, M6, M12

| 0 | D5 | D10 | D15 | D20 | D28 |
Posttransplant follow-up

- 5 to 15% of patients will develop antibody-mediated rejection: 99% will occur within the first month posttransplant
  - Afterwords: ACCOMODATION
  - 5 to 10% of ACR
  - No steroids stop (25% of ACR)
### Some IVIg contain isoagglutinins!

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<th>IVIG</th>
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**Abbreviations:** Titer Pre, AB0i antibody titer before IVIG administration; Titer Post, AB0i antibody titer after IVIG administration.

† IVIG administration was performed during IA treatment explaining the decline in AB0i antibody titers after IVIG administration.

Renner FC et al. Transplant Proc. 2010;42:4003-4005
Comparison of long-term results in ABO incompatible and ABO compatible kidney transplantation
Cumulative incidence of (A) death-censored graft survival and (B) patient death in living-donor recipients of an ABO-incompatible graft, matched controls receiving an ABO-compatible graft, or all ABO-compatible transplants from centers that performed at least five ABO-incompatible grafts during the study period (‘center control’ group) (Kaplan-Meier estimates). P values according to the log-rank test.

Opelz G. et al. Transplantation 2015;99(2):400-404
Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers (2)

Cumulative incidence of death-censored graft survival in living-donor recipients of an ABO-incompatible graft according to whether ABO antibody reduction was performed by adsorption columns or plasma exchange (Kaplan-Meier estimates). P values according to the log-rank test.

Opelz G. et al. Transplantation 2015;99(2):400-404
Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers (3)

Cumulative incidence of death because of infection in living-donor recipients of an ABO-incompatible graft, matched controls receiving an ABO-compatible graft, or all ABO-compatible transplants from centers that performed at least five ABO-incompatible grafts during the study period (“center control” group) (Kaplan-Meier estimates). P values according to the log-rank test.

Opelz G. et al. Transplantation 2015;99(2):400-404
**Graft survival**

**ABOi vs. ABOc**

Log-rank test: 0.632

<table>
<thead>
<tr>
<th></th>
<th>ABOI &amp; Splenectomy</th>
<th>ABO-I &amp; Rituximab</th>
<th>ABO-C</th>
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<td>9 year</td>
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ABO-I Spx: splenectomy  
ABO-I Rit: Rituximab injection  
ABO-C: ABO-Compatible

Rejection rate

Within 6 months

After 6 months

Incidence of *de novo* anti-HLA antibodies

![Graph showing incidence of *de novo* anti-HLA antibodies.](image)

- ABO-I: 1 (2%) (n=45)
- ABO-I&RIT: 1 (2%) (n=57)
- Control: 17 (20%) (n=83)

ABO incompatible kidney transplantation: patient survival at TWMU

Log-rank test: <.001

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<th>Period</th>
<th>5 year</th>
<th>10 year</th>
<th>15 year</th>
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</table>
Graft survival (1989-2013)
Era of modern immunosuppression

(A) Graft survival (non-censored for death) for transplantation in 1989 to 2004

Log-rank test: p=0.026
Adjusted HR: 1.56 (95% CI: 1.04 to 2.34) p=0.030

Number at risk
ABO-CLKT: 452, 440, 435, 428, 411, 395, 381, 373, 364, 353
ABO-ILKT: 103, 88, 88, 84, 83, 77, 76, 73, 71

(B) Graft survival (non-censored for death) for transplantation in 2005 to 2013

Log-rank test: p=0.279
Adjusted HR: 1.38 (95% CI: 0.59 to 3.22) p=0.455

Number at risk
ABO-CLKT: 333, 329, 278, 229, 186, 143, 111, 78, 46, 22
ABO-ILKT: 144, 142, 114, 95, 68, 49, 34, 22, 12, 5

Okumi, AJT 2016
Patient survival (1989-2013)
Era of modern immunosuppression

(C) Patient survival for transplantation in 1989 to 2004

- Log-rank test: p=0.919
- Adjusted HR: 0.84 (95% CI: 0.28 to 2.52) p=0.753

Number at risk
ABO-CLKT 452 449 448 447 444 440 438 433 431 429
ABO-ILKT 103 100 100 100 99 99 96 96 95 94

(D) Patient survival for transplantation in 2005 to 2013

- Log-rank test: p=0.532
- Adjusted HR: 0.52 (95% CI: 0.11 to 2.49) p=0.414

Number at risk
ABO-CLKT 333 329 280 232 190 146 114 80 49 24
ABO-ILKT 144 144 117 98 72 53 26 25 13 6

Okumi, AJT 2016
Tyden protocol (Sweden)

Follow-up: 3.4 ± 1.6 y (ABOi) and 4 ± 1.1 y (ABOc)
One-year kidney histology: ABOi vs. ABOc
One-year kidney histology: ABOi vs. ABOc

ABOi kidney transplantation patients’ and grafts’ survival: IA vs. apheresis

Lo et al. Transplantaiton 2015

### Patient survival

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<th>Study</th>
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### Graft survival

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### Immunoadsorption

N=4, I² = 0%

### Apheresis

N=21, I² = 7%
# ABOi kidney transplantation patients’ and grafts’ survival: Rituximab vs. splenectomy

**Patient survival**

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**Graft survival**

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**Rituximab**

$N=17$, $I^2 = 0\%$

**Splenectomy**

$N=12$, $I^2 = 3\%$

**Rituximab**

$N=16$, $I^2 = 14\%$
The graft survival rate in the AMR group was significantly lower than in the non-AMR group. (AMR vs. non-AMR, respectively; 3 years: 84 vs. 100%; 5 years: 84 vs. 95%; 8 years: 49 vs. 95%; p = 0.009).
The mean serum creatinine concentration was significantly higher in the AMR group than in the non-AMR group at all time points except year 8 (p < 0.05, Student's t-test).
Complications of
ABO-i kidney transplantation
Early clinical complications after ABO-incompatible live-donor kidney transplantation: a national study of medicare-insured recipients

Kaplan-Meier estimates of infectious complications and hemorrhage frequencies over periods of 0 to 90 days and 91 to 365 days, according to blood type compatibility. ABOi, ABO incompatible; A2i, A2 incompatible; ABOc, ABO compatible. P values versus ABOc, *0.0001 to <0.05, ‡<0.0001.

ABO-i vs. ABO-c kidney transplantation: acute rejection and surgical complications

Number of rejections in ABOi and ABOc recipients. The number of patients experiencing one or more rejections (including borderline cases with impaired renal graft function) diagnosed in any of the three protocol biopsies or biopsies on cause did not differ between ABOi and ABOc recipients, while the number of subclinical rejections showed a higher tendency in ABOi recipients (non-significant).

Incidence of SCs in ABOi and ABOc recipients. The number of patients experiencing one or more SC was higher in ABOi transplant recipients as compared to ABOc recipients (non-significant).
Infectious complications after ABO-i kidney transplantation (1)

Incidence of infectious complications in ABOi and ABOc recipients One or more episodes of viral infections, including CMV, HSV, VZV and BKV infections occurred significantly more often in ABOi recipients as compared to ABOc recipients (P=0.038).

Habicht A, et al. NDT 2011;26:4124-4131
Infectious complications after ABO-i kidney transplantation (2)

Binary logistic analysis for pooled infectious complications

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P-value</td>
<td>HR</td>
</tr>
<tr>
<td>ABO-status</td>
<td>0.283</td>
<td>0.095-0.842</td>
<td>0.02*</td>
<td>0.319</td>
</tr>
<tr>
<td>Previous Tx</td>
<td>1.065</td>
<td>0.232-4.888</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>SCs</td>
<td>0.222</td>
<td>0.065-0.756</td>
<td>0.02*</td>
<td>0.475</td>
</tr>
<tr>
<td>Rejections (overall)</td>
<td>0.204</td>
<td>0.055-0.756</td>
<td>0.02*</td>
<td>0.232</td>
</tr>
<tr>
<td>Rejections (clinical)</td>
<td>0.393</td>
<td>0.055-2.230</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Rejections (subclinical)</td>
<td>n.s</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)All variables were included as categorical variables (yes/no),
Abbreviations: CI = confidence interval ; HR=hazard ratio ; n.s. = non-significant ; PRA = preformed antibodies.
Infectious complications after ABO-i kidney transplantation (3)

Incidence of BK nephropathy in ABOi and ABOc recipients. The number of patients with a biopsy-proven BK nephropathy was higher in the ABOi group as compared to the ABOc group.
Higher cost for ABOi vs. ABOc
We started in April 2011 - December 2015

- We use the Tyden protocol (pretransplant PP + immunoadsorption with Glycorex® columns, or semi-specific columns in case of associated HLAi) aiming at isoagglutinin titer below ¼

- 54 patients
  - 44 ABOi
  - 10 ABOi HLAi
### Toulouse: Outcome (N=54)

<table>
<thead>
<tr>
<th></th>
<th>ALL (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ survival</td>
<td>100%</td>
</tr>
<tr>
<td>Grafts’ survival</td>
<td>93%</td>
</tr>
<tr>
<td>Acute rejection</td>
<td></td>
</tr>
<tr>
<td>- AMR</td>
<td>15 (27.8%)</td>
</tr>
<tr>
<td>- ACR</td>
<td>9 (16.7%)</td>
</tr>
<tr>
<td>- ACR</td>
<td>11 (20.4%)</td>
</tr>
<tr>
<td>Mean Follow-up (days)</td>
<td>699±514</td>
</tr>
</tbody>
</table>

Patient 1: vascular thrombosis at day 0; Second transplantation; ABOi HLAi; Anti A ¼, DSA MFI < 5000 the day of transplantation, CDC XM neg

Patient 2: TMA at day 5 treated by Eculizumab, Poor kidney function; graft loss at month 12.

Patient 3: TMA 2 years after transplantation (non compliance?)

Patient 4: Bad kidney function since transplantation. Graft loss at 2 years
Toulouse: Kidney function

GFR mL/min

Day 5 | Day 15 | Day 30 | Month 3 | Month 6 | Month 12 | Month 18 | Month 24
• ABO incompatible living-(un)related kidney transplantation provides in the long-term very good results, even BETTER to those obtained with ABO compatible living-(un)related kidney transplantation

• Alternative therapy to pair exchange programs

• Posttransplant immunosuppression relies on Tac + MPA; however, MPA could be REPLACED by 2 months (or so) posttransplantation by mTOR-inhibitors in the case of BKV infection or in order to decrease the rate of viral infections.
Q1: ABO incompatible kidney transplantation

- Donor O / Recipient A
- Donor AB / Recipient A
- Donor O / Recipient AB
- Donor A / Recipient AB
Q1: ABO incompatible kidney transplantation

- Donor O / Recipient A
- Donor AB / Recipient A
- Donor O / Recipient AB
- Donor A / Recipient AB

✓ Donor AB / Recipient A
Q2: Immunosuppression for ABOi KT

- Systematic apheresis/Immunoadsorption
- Splenectomy
- Rituximab
- Steroid free regimen
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- Systematic apheresis/Immunoadsorption
- Splenectomy
- Rituximab
- Steroid free regimen
Q3: ABOi vs ABOc

- Higher long-term graft survival for ABOi KT
- Higher incidence of AMR in case of ABOi KT
- Positive C4d staining is a predictive factor for graft loss
- Isoagglutinin level rebound is systematic after transplantation
Q3: ABOi vs ABOc

- Higher long-term graft survival for ABOi KT

✓ Higher incidence of AMR in case of ABOi KT

- Positive C4d staining is a predictive factor for graft loss

- Isoagglutinin level rebound is systematic after transplantation
Q4: Complications after ABOi KT

- More frequent bleeding
- Less BK virus infection
- More fungal infections
- Similar complications in ABOc and ABOi KT
Q4: Complications after ABOi KT

- More frequent bleeding
- Less BK virus infection
- More fungal infections
- Similar complications in ABOc and ABOi KT
Thank you for your attention.