ABO incompatible kidney transplantation from a living donor: an effort to establish a common Belgian protocol in the context of the Belgian Transplantation Society

Laure Collard, ULG
Alain Le Moine, ULB
Michel Mourad, UCL
Maarten Naesens, KUL
Lissa Pipeleers, UZB
Steven Van Laecke, Gent
Daniel Abramowicz, UZA
Outline of the presentation

1. Why a Belgian ABOi protocol?
2. What numbers/proportions can we expect?
3. ABOi Tx: biology and results
4. Principles of successful ABOi TP
5. The first draft of the Belgian ABOi protocol
6. Future hurdles to be tackled
LIVING DONOR TRANSPLANTS 2017

- Kidney
- Liver
Up to 30% of potential LD are excluded because of ABOi

Karpinski Am J Kidney Dis 2005; 47:317
- Anti-ABO Abs: both « natural » and acquired (« immune »)
- Both IgG (the most important in TP) and IgM

<table>
<thead>
<tr>
<th>TYPE A</th>
<th>TYPE B</th>
<th>TYPE AB</th>
<th>TYPE O</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1: 36%</td>
<td>B: 9%</td>
<td>AB: 4%</td>
<td>O: 41%</td>
</tr>
<tr>
<td>A2: 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Expression des Ag ABO dans le rein

- Artères, veines
- Capillaires
  - Glomérulaires
  - Capillaires péritubulaires
- Membranes basales des cellules épithéliales des tubes

➔ Rejet hyperaigu humoral si transplantation en présence d’Acs anti-ABO
Accommodation: limited Ct activation without graft damage

Systematic Tx biopsy, day 21, nl Tx function, anti-A: 1/32

Light MO  C4d staining
PRE-TRANSPLANT DESENSITISATION

1. ANTIBODY REMOVAL
2. ASSAY AB TITERS
3. PREVENT AB (RE)SYNTHESIS
4. IMMUNOSUPPRESSION

‘APHERESE’

MANY DIFFERENT PROTOCOLS, NO SINGLE RCT!
DESENSITISATION PROTOCOL

Rituximab

Apheresis

Transplantation

'On demand' antibody depletion

Induction therapy

Anti-A/B antibody level

Baseline

Target

(< 1:4 / 1:8)

Titre reduction

Baseline immunosuppression

Antibody recurrence

Accomodation

Time

Nature Reviews | Nephrology

Böhmig, G. A. et al. (2015) Strategies to overcome the ABO barrier in kidney transplantation

Nat. Rev. Nephrol. doi:10.1038/nrneph.2015.144
Three-Year Outcomes Following 1420 ABO-Incompatible Living-Donor Kidney Transplants Performed After ABO Antibody Reduction: Results From 101 Centers

Gerhard Opelz,1 Christian Morath,2 Caner Süsal,1 Thuong Hien Tran,1 Martin Zeier,2 and Bernd Döhler1

FIGURE 1. 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.
The Belgian ABOi kidney transplantation protocol

Version 3 18/10/2018
Four meetings: 17/05/2017, 18/10/2017, 20/3/2018, 11/7/2018 (meeting with Fresenius, Miltenyi bioyech, Glycosorb)

Drs. Laure Collard (ULG), Lissa Pipeleers (UZB), Steven Van Laecke (UZG), Maarten Naessens (KUL), Alain Le Moine (ULB), Michel Mourad (UCL), Daniel Abramowicz (UZA)

1. Inclusion criterias (all)
2. LDEP (MN, LC)
3. Do we need Rituximab for ABO incompatible (ABOi) transplantation? (ALM, DA)
4. Which apheresis technique will be used? (LC, MM)
5. What titer of anti-A/B antibodies should be achieved? Which method should be used? (SVL, LP)
6. Immunosuppressive therapy (ALM, DA)
7. Do we need Ivig for ABOi KTR? (ALM, DA)
8. Is there a need for post-transplant AB titers FU and systematic biopsies? (SVL, MM)
9. Database ABOi Tx (MN, LP)
Inclusion criteria

• Living donors A, B, or AB; recipient O, A, or B; HIV neg; crossmatch negative, signed informed consent.

• The working group advises inclusion of patients in need of a first transplantation, with a PRA < 30% (ET), DSA negative. However, inclusion of patients will be performed according to local practice and falls under the responsibility of the center.
Algorithm LDEP/ABOi protocol

Every living donor-recipient pair in which the transplant cannot be performed because of ABO incompatibility should be informed about the possibility to be included in:

→ the nationwide LDEP program
→ an ABOi protocol.

**Pre-emptive indication:** ABOi couples should be proposed to enroll in the LDEP program, and wait for a match, until dialysis is imminent (within the following three months) and an ABOi transplant can be scheduled. The number of LDEP runs is not relevant here.

**Patients already in dialysis:** ABOi couples should be proposed to enroll in the LDEP program, and if one run is not successful, or if the run is not scheduled within a reasonable time frame (more than 2 months), the couple should be offered ABOi transplantation.
Use of Rituximab

A single dose of Rituximab (Mab-Thera) drip infusion, 375 mg/m², approximately 1 month prior to transplantation is administered.

Rituximab can be infused through a peripheral vein or through the venous line of an a-v fistula.

Start with 50mg/h, if well tolerated increase drip infusion to 100mg/h after 30 min, 200mg/h after 60 min, and 400mg/h after 90 min.

In order to avoid adverse effects, use a pre-medication with: paracetamol, 1g po, 30-60 min before infusion; diphenhydramin 25mg po, or an equally potent anti-histaminicum, 30-60 min before infusion.
How should AB blood titers be measured?

<table>
<thead>
<tr>
<th>Donor blood group</th>
<th>Recipient blood group</th>
<th>Tube titer</th>
<th>Ortho titer</th>
<th>Diaimed gel card titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>O</td>
<td>32</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>A1</td>
<td>O</td>
<td>64</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>A1(^c)</td>
<td>B</td>
<td>16</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>A2</td>
<td>O</td>
<td>32</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2(^b)</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

→ Large inter-assays variations
→ Need to agree between centers on the method to be used
What titer of anti-A/B abs should be achieved?
Which method should be used?

- Sample analysis at local blood bank laboratory of the Red Cross
- Measure IgG and IgM
- Column agglutination Gel cards methods (Bio Rad®, http://www.bio-rad.com)
- Scheme for Ab-titer measurement
  - At referral (consider exclusion if titer > 1:1024 )
  - After administration of Rituximab, before apheresis
- **Target titer before transplantation ideally ≤ 1:4 on 2 consecutive days preceeding the transplantation** (taken into account the kinetics of the antibody titer relative to apheresis).
- If not achievable within a reasonable amount of apheresis sessions (≤ 8), **a titer of 1:8 on the day of transplantation seems acceptable.**
- Before and after each apheresis treatment.
- Post-Tx, in decreasing frequency with time
Immunosuppressive protocol

- **Steroids (prednisone or methylprednisolone):** At start of apheresis: 20 mg/d po; day 0: 250 mg iv; day 1: 125 mg iv; day 2-7: 40 mg po; day 8-28: 20 mg po; day 29-60: 15 mg po; day 61-180: 10 mg; after day 180: 5 mg. The working group does not advise steroid withdrawal, but immunosuppressive regimens belongs to center responsibilities.

- **Tacrolimus** 2 x 0.10 mg/kg/d, starting one week prior to planned transplantation. Dose adjustment according to trough levels is suggested as follows: day –7 to 90: 8-12 ng/ml; day 91 to 365: 6-10 ng/ml; day > 365: > 5 ng/ml. (Advagraf ® can be used according to local practice)

- **Mycophenolate mofetil (or equivalent doses of Myfortic):** 2 x 500 mg/day, starting one week prior to planned transplantation; 2x1000 mg/day from the day of Tx until the end of month 1; then 2x750 mg/day (according to center practice).

- **Simulect (basiliximab):** 20 mg, day 0 and day 4. The working group recommends caution when using a T-cell depleting agent in B-cell depleted patients.
### Do we need Ivig?

<table>
<thead>
<tr>
<th>Center</th>
<th>Apheresis technique</th>
<th>Ivig use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tokyo Women’s hospital center, Japan</td>
<td>DFPP</td>
<td>No</td>
</tr>
<tr>
<td>Johns Hopkins Hospital, Baltimore, USA</td>
<td>Plasma exchanges (PE)</td>
<td>Yes</td>
</tr>
<tr>
<td>University Medical Center, Freiburg, Germany</td>
<td>Immunoadsorption and PE</td>
<td>No</td>
</tr>
<tr>
<td>Karolinska University Hospital, Sweden</td>
<td>Immunoadsorption</td>
<td>Yes</td>
</tr>
<tr>
<td>Cedars-Sinai Medical Center, LA, USA</td>
<td>PE</td>
<td>Yes</td>
</tr>
</tbody>
</table>

As the clinical results of these various centers are impossible to compare in detail, all claiming excellent patient and graft survival, one comes to the conclusion that **Ivig does not seem to be an obligatory component of ABOi KTR, and certainly not when immunoadsorption columns are used.** Therefore, **we do not recommend the routine use of Ivig for ABOi KTR.**
Which apheresis technique will We use?

Number of ABOi Kidney Transplants

JAPAN (DFPP) > 2000 (as to year 2010)
USA (PE) > 1000 (as to year 2011)
Germany (IA) > 1000 (as to year 2012)…..

REGARDLESS OF THE TYPE OF APHERESIS

DFPP, Double-Filtration PlasmaPheresis
PE, standard Plasma Exchange
IA=ImmunoAdsorption (Selective or Non-selective)
GLYCOREX TRANSPLANTATION AB

Offer

Offer No/Customer No: 6683 20011603
Offer date: 2018-07-13

Delivery address:
Universitair Ziekenhuis Antwerpen
Wilrijkstraat 10
2650 Edegem
Belgium

Invoice address:
Universitair Ziekenhuis Antwerpen
Wilrijkstraat 10
2650 Edegem
Belgium

Your reference: Prof. Dr. Daniel Abramowicz
Our reference: Cecilia Höst

Your ref. No
Terms of delivery: ExWorks
Valid until: 2019-07-13
Terms of payment: 20 days net

Transported by: UPS
Penalty interest: 18,00 %

<table>
<thead>
<tr>
<th>Article No</th>
<th>Denomination</th>
<th>Quantity</th>
<th>Unit</th>
<th>Unit price</th>
<th>Discount</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>7601-1</td>
<td>GlycoSorb A or</td>
<td>75</td>
<td>unit</td>
<td>4 095,00</td>
<td>31,5 %</td>
<td>210 375,00</td>
</tr>
<tr>
<td>7602-1</td>
<td>GlycoSorb B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SINGLE USE ONLY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Is there a need for post-transplant AB titers FU and systematic biopsies?

- **Postoperative titers** are measured daily the first 5 days, second daily until day 14, and then weekly for the first 2 months, at month 3, 6, 12 or after decline of kidney function.

- The aimed targets should be titers ≤1:16 the first week and ≤1:32 the second week (card method) **above which plasmapheresis or immunoadsorption is needed**.

- **Protocol biopsies** occur at the discretion of the treating physician. The histological presence of C4d without signs of rejection is common and of uncertain significance.
The Belgian ABOi protocol: hurdles to be tackled

1. Finalize the protocol (due early 2019)
2. Discuss and obtain the reimbursement (RIZIV/INAMI) of RTX, IgV, ABO titers, apheresis (PP, DFPP, glycosorb columns).
3. Contact with Dr. Joel Daems, Transplantation group/CRM (first meeting in June 2018)

Thank you for your attention!
Bedankt voor uw aandacht!
Merci d’vosse attencion!