Update on the treatment of Antibody-Mediated Rejections

D. Glotz
The changing picture of Rejections
Antibody Mediated Rejection

Kidney

- Histological Lesions
  - ATN
  - CPT, glom, thromboses
  - Arteritis
- C4d positive
- Donor specific Antibodies

Racusen AJT 2003
Antibody Mediated Rejection

Kidney

D. Nochy
### C4d positivity in various Tx centers

<table>
<thead>
<tr>
<th>Authors</th>
<th>Biopsies/Pts</th>
<th>indication</th>
<th>C4d+ (% Pt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feucht 1993</td>
<td>93/93</td>
<td>Renal failure</td>
<td>46%</td>
</tr>
<tr>
<td>Lederer 2001</td>
<td>310/218</td>
<td>Renal failure</td>
<td>46%-72%</td>
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<tr>
<td>Regele 2001</td>
<td>102/61</td>
<td>Renal failure</td>
<td>51%</td>
</tr>
<tr>
<td>Bohmig 2002</td>
<td>113/58</td>
<td>Renal failure</td>
<td>28%</td>
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<tr>
<td>Nickeleit 2002</td>
<td>398/265</td>
<td>Renal failure</td>
<td>35%</td>
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<tr>
<td>Herzenberg 02</td>
<td>126/93</td>
<td>Rejection</td>
<td>37%</td>
</tr>
<tr>
<td>Mauiyyedi 02</td>
<td>67/67</td>
<td>Renal failure</td>
<td>30%</td>
</tr>
<tr>
<td>Regele 2002</td>
<td>213/213</td>
<td>Renal failure</td>
<td>34%</td>
</tr>
<tr>
<td>Sund 2003</td>
<td>37/37</td>
<td>Protocol</td>
<td>30%</td>
</tr>
<tr>
<td>Koo 2004</td>
<td>96/48</td>
<td>Protocol</td>
<td>13%</td>
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</tbody>
</table>
Prophylaxis of AMR: IVIg

Kazatchkine NEJM 2001
Mechanisms of action of IVIg

Innate immunity
- DC-mediated T-cell activation ↓
- Endocytosis ↓
- Pro-inflammatory cytokine production ↓
- Anti-inflammatory cytokine production ↑
- DC differentiation ↓
- Expression of MHC class II and co-stimulatory molecules ↓
- Expression of CD1d ↑
- NK-mediated ADCC ↑
- Expression of activating FcγRs ↓

Adaptive immunity
- T-cell activation and proliferation ↓
- IL-2 production ↓
- T-cell apoptosis ↑
- T-cell differentiation ↓

IVIg

- Induce changes in NK-cell trafficking from blood to tissue
- NK-cell activation ↑
- Cytokine production and degranulation ↑
- Anti-tumour activity ↑

- Expression of inhibitory FcγRIIB ↑
- Blockade of activating FcγRs
- Macrophage activation ↓
- Production of proinflammatory cytokines ↓
- Production of IL1-RA ↑
- Expression of activating FcγRs ↓
- Expression of IFN-γR2 ↓

- Neutrophil death via Siglec ↑
- Neutrophil activation by IgG monomers blocking FcγRs ↓
- Neutrophil activation by IgG dimers binding FcγRs or by ANCA ↑
- Neutrophil adhesion to endothelium ↓

Key:
- IgG in IVIg preparations
- Cytotoxic granules
- Activating FcγR
- Antigen
- B-cell receptors on B cells
- Unidentified sialic-acid-specific
- Inhibitory FcγR receptor

Durandy Clin Exp Immunol 2009
IVIg at the time of Transplantation

Pediatric CMV recipients

Bunchman Clin Transpl 1997
IVIg at the time of Transplantation

Cadaveric re-transplants

- 41 patients
- Immunized or not
- Quadruple IS
- IVIg 0.4 gr/Kg for 5 days
IVIg at the time of Transplantation

Peraldi Transpl 1996

Cadaveric re-transplants
Prophylaxis of AMR
ATG/IVIg in DSA +, XM - pts

Bächler AJT 2010
Prophylaxis of AMR

ATG/IVIg vs ATG/IVIg/Ritux/PP

Peak serum DSA MFI
- Class I or II DSA_{max} MFI
  - Class I MFI_{max} DSA: 8747 ± 779
  - Class II DFI_{max} DSA: 5314 ± 782
- % positive class I or II DSA
  - 36/36 (100)

Day 0 serum DSA MFI
- Class I or II DSA_{max} MFI
  - Class I MFI_{max} DSA: 5314 ± 807
  - Class II MFI_{max} DSA: 2457 ± 634
- % Positive class I or II DSA
  - 26/27 (96.2)

Outcome
- Acute humoral rejection: 7 (19.6)
- Patient death at last follow-up: 1 (2.7)
- Graft lost at last follow-up: 4 (11.1)
- Mean follow-up: 35.4 ± 16.7

Transplant biopsy
- DSA testing
- GFR measurement

Loupy Transpl 2010
After transplantation

Treatment of established rejection

- Acute AbMR
- Sub-clinical AbMR
- Chronic AbMR
Subclinical-AMR

Function

Pathology

Usefulness of Abs/screening biopsies+++
Subclinical-AMR definition

Patient in a steady state: Stable GFR

Evidence for Ab injury: glomerulitis + / PTC+

Evidence for Ab action in PTC: C4d+

Evidence for serologic Ab: DSA+

Gloor et al; Haas et al; Lerut et al
Adapted Treatment is essential

<table>
<thead>
<tr>
<th></th>
<th>OKT3</th>
<th>IVIg</th>
<th>PP/IVIg</th>
<th>Ritux/PP</th>
<th>PP/IVIg/Ritux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts</td>
<td>43</td>
<td>21</td>
<td>16</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Pt Surv</td>
<td>95%</td>
<td>84%</td>
<td>100%</td>
<td>100%</td>
<td></td>
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<tr>
<td>G Surv</td>
<td>57%</td>
<td>72%</td>
<td>81%</td>
<td>75%</td>
<td>92%</td>
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</tbody>
</table>
Antibody Mediated Rejection Treatment

High dose IVIg

- **10 patients with severe AR / 4 DSA+**
- **100% response short term**
- **fall of anti-HLA Abs titers**

- **17 patients**
- **AR aux steroid- resistant / anti-lymphocyte Abs**
- **Patients Survival 18 months : 94%**
- **Graft Survival 18 months : 71%**

- **71.5% success, 1 death**
- **Mean Follow-up : 30 ± 20 months**
- **SCr end of FU : 187 µmol/L**

- **Jordan SC et al., Transplantation 1998**
- **Luke PP et al., Transplantation 2001**
- **H.E.G.P./Saint-Louis Lefaucheur AJT 2007**
Antibody Mediated Rejection Treatment

IVIg/PP treatment

- 16 patients
- 100% StR, 50% AbR
- Graft survival 1 year: 81% (84%)

Rocha, Transpl 2003
Impact of a single agent difficult to judge...

Kapotzas, Clin Tx 2008
Effect of PE alone on Ig synthesis

Table 3
In vitro immunoglobulin production with plasma exchange

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Treatment</th>
<th>IgG No.</th>
<th>IgM No.</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>No. 1</td>
<td>No. 5</td>
</tr>
<tr>
<td>1</td>
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<td>70 a</td>
<td>100</td>
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<td>2</td>
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<td>7</td>
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<td>8</td>
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<td>210</td>
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<tr>
<td>9</td>
<td></td>
<td>110</td>
<td>220</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>130</td>
<td>440</td>
</tr>
</tbody>
</table>

\[126 \pm 73^b \quad 332 \pm 267^b \quad 48 \pm 20^b \quad 429 \pm 571^b \]

\[P < 0.05^* \quad P < 0.001^*\]
IVIg +/- Plasmapheresis

N=13
P=0.044

N=11

FIG. 1. Graft survival. Patients receiving the plasmapheresis (PP) and intravenous immunoglobulin (IVIg) combination had better one-year graft survival than those treated using only PP. $P = 0.044$. 

Slatinska, Ther Aph Dial 2009
Antibody Mediated Rejection Treatment
The “Marrakesh” protocol

- Bx
- DSA
- PP/IVlg
- Ritux
- IVlg high dose
- 0 1 2 3 4 5

- 4 PP/low dose IVlg
- Ritux 375 mg/m²
- IVlg 2gr/Kg
Comparison of Combination Plasmapheresis/IVIg/anti-CD20 versus High-Dose IVIg in the Treatment of AMR

- **Group A:** High-dose intravenous immunoglobulin (IVIg) regimen
  - 01/2000-12/2003
  - N=12 pts

- **Group B:** Plasmapheresis (PP) / IVIg / anti-CD20 (PP/IVIg/anti-CD20) regimen
  - 01/2004-12/2005
  - N=12 pts

Lefaucheur, A.J.T. 2009
Kaplan Meier plot of graft survival in patients with AMR according to treatment type

Lefaucheur, A.J.T. 2009
DSA Monitoring is key

The absence of decrease of DSA post-treatment is associated with poor prognosis

24 patients, DSA at rejection and 3 months post TT

- Good evol. (n=18)
- Bad evol. (n=6)

Lefaucheur, A.J.T. 2009
High levels of DSA post-treatment are associated with a higher risk of graft loss.

Receiver operating characteristic (ROC) curve for the MFI_{max} of DSAs detected 3 mo post-AMR associated with GFR \leq 15 \text{mL/min/1.73m}^2 at 36 months post-AMR.

MFI_{max} > 5000
Se 100%
Sp 77.8%
DSA Monitoring is key

The absence of a fall of at least 50% of DSA post-treatment is associated with poor prognosis

16 patients, DSA 14 days post diagnostic biopsy

<table>
<thead>
<tr>
<th></th>
<th>More than 50% decrease of DSA</th>
<th>Less than 50% decrease of DSA</th>
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<tbody>
<tr>
<td>Rej. reversal (creat)</td>
<td>90%</td>
<td>83%</td>
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<tr>
<td>G.S. 2 years</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>G.S. 4 years</td>
<td>100%</td>
<td>20%</td>
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Everly WTC 2008
Bortezomib

In vitro...

Apoptosis of PC in vitro

Perry, AJT 2009
Bortezomib

In vitro....
Bortezomib

In vitro....

Diwan, transpl 2011
Bortezomib

In vivo....

<table>
<thead>
<tr>
<th>SI no</th>
<th>BL BFXM</th>
<th>PT BFXM</th>
<th>PPE BFXM</th>
<th>BL MFI</th>
<th>PT MFI</th>
<th>PPE MFI</th>
<th>BL BFXM</th>
<th>PT BFXM</th>
<th>PPE BFXM</th>
<th>BL MFI</th>
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<td>556</td>
<td>528</td>
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<td>13570</td>
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<td>9**</td>
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</tbody>
</table>

**TABLE 3.** Proteasome inhibition potentiates antidonor HLA antibody reduction with plasma exchange

<table>
<thead>
<tr>
<th>Category</th>
<th>Bortezomib+PE group (n=5)</th>
<th>PE only group (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>a No. PE (mean±SD)</td>
<td>11.4±2.7</td>
<td>11.6±3.9</td>
<td>0.9</td>
</tr>
<tr>
<td>b Baseline-post-PE BFXM (mean±SD)</td>
<td>272±92.1</td>
<td>95.4±72.2</td>
<td>0.008</td>
</tr>
<tr>
<td>c % Change in BFXM CS (mean±SD)</td>
<td>49.1±14.9</td>
<td>17.7±12.5</td>
<td>0.005</td>
</tr>
<tr>
<td>d Achieving a channel shift &lt;300</td>
<td>3 (60%)</td>
<td>0 (0%)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

(a) Similar numbers of plasma exchanges were performed in the bortezomib-treated patients compared with the control group, P=0.9. (b) Bortezomib treatment before plasma exchange resulted in a greater reduction in serum donor-specific alloantibody compared with untreated controls (P=0.008). (c) The percentage change in donor-specific alloantibody also was greater (P=0.005).

HLA, human leukocyte antigen; SD, standard deviation.

Diwan, transpl 2011
Bortezomid

Treatment of rejection

- 1.3 mg/m² x 4
- 6 patients, 6 successes.....

Everly, Transpl. 2008
Bortezomib

Treatment of rejection

• 1.3 mg/m² x 4
• 20 patients, GS 9.5 months 85%.....

Flechner, Transpl. 2010
Bortezomid

In vivo.... ????

5 pts with AMR/ACR

Everly Trans Proc 2009

11 pts without AMR/ACR, 8 DSA

Trivedi Transpl 2009
Bortezomid

In vivo....????
Figure 1  A simplified scheme of the complement activation cascade shows that C3 and C5 are critical convergence points of four activation pathways and indicates potential targets of anti-inflammatory drugs. Inhibitors targeting C5 may impact activation of all four pathways and offer advantages over C3 inhibitors, most notably the generation of C3b, a key component of the innate immune response. Inhibitors of C5aR signaling seem to have a different mechanism of action and associated risk-benefit profile compared with those that block cleavage of C5 to generate C5a and C5b-9.
C5 inhibition

Monoclonal anti C5 Ab: Eculizumab

- 26 patients
- **Inclusion**: positive B cell flow XM
- **Success**: diminution of B cell flow XM
- PP pre-Tx if B cell flow XM > 300
- Eculizumab: D0, weeks 1, 2, 3, 4.... and more
- Only 2 rejections

Historical control group (n=51): 41% AMR

Stegall, Gloor
C5 inhibition

Locke AJT 2009
C5 inhibition: CAD Tx

- PP
- Ritux
- Velcade
- Soliris
- Splenectomy
C5 inhibition: CAD Tx

- Ritux
- Splenectomy
- Velcade
- Soliris
C5 inhibition: LD Tx

- LD Tx
- IVIg
- Soliris
- Cy
- HD
- Bx
- Bx
- Bx

Graph showing changes over time with various markers:
- creat
- DR4
- DR53
- DQ8
- A24
- B7

Time scale: 0 to 80

Markers: IVIg, Cy, Soliris
C5 inhibition: LD Tx

Soliris
BAFF, APRIL, TACI and co...