Desensitization in the setting of HLA incompatible kidney transplantation

Pr. Lionel ROSTAING
Chairman,
Departement of Nephrology and Organ Transplantation
CHU Rangueil, Toulouse, France
rostaing.l@chu-toulouse.fr
**Definition**:

- Presence at pretransplant of anti-HLA allo-antibodies directed against the recipient (donor-specific alloantibody: DSA)

- DSA can be detected by:
  - Complement dependent lymphocytotoxicity (CDC)
  - Elisa
  - Luminex® (expressed by mean fluorescence intensity – MFI-, from 1,000 up to 20,000)

- Cross-match can be positive
  - By microlymphocytotoxicity (CDC)
  - By flow cytometry (FCM)

- Cross-match can be negative, i.e. in the case where MFI of DSA is low ($\approx < 6000$)

- DSA can or cannot bind C1q or C3d
Consequences of DSA in KTx patients

- Increased risk of antibody-mediated rejection (AMR) (acute and/or chronic)
- Increased risk of transplant glomerulopathy
- Increased risk of allograft loss
Natural History of antibody mediated rejection (AMR)

**Function**
- Acute clinical ABMR
- Indolent ABMR
- Graft dysfunction

**Histopathology**
- Endothelial injury
- Peritubular capillaritis
- Glomerulitis
- Persisting microvascular inflammation

**DSAs**
- Complement activation
  - Preformed DSAs
  - ENDATs
- Persisting or de novo DSAs

**ENDATs**: endothelial-associated transcripts
**IF/TA**: interstitial fibrosis/tubular atrophy

Loupy et al. Nat Rev Nephrol 2012
Long-term outcome of patients with XM (+)

- Case Controlled study: 102 KT XM (+) and 204 KT XM (-)
- At baseline:
  - 40% CDC XM +
  - 35% anti-class I DSAs
  - 20% anti-class II DSAs
  - 45% anti-class I and II DSAs
- Desensitization for XM (+) patients:
  - PP / Low dose IVIg / Splenectomy (n=16)
  - PP/ High dose IVIg (n=48)
  - High dose IVIg (n=21)
  - None: 17
- Immunosuppression: ATG/Tac/MMF/Cs

Bentall et al., AJT 2013
Patients’ and Grafts’ survivals: XM (+) vs. XM (-)

A 5-year Patient Survival

B 5-Year Overall Graft Survival

C Graft Survival by Crossmatch Assay (CDC+ vs CDC-/FXM+)

D Graft Survival by Donor-Specific HLA Antibody Specificity

Bentall et al., AJT 2013
Harmful impact of low-levels DSA even with CDC XM (–) and FCXM (–)

Risk of AMR:
OR 1.98, IC 95% (1.36-2.89), p<0.001

Risk of graft loss:
OR 1.76, IC 95% (1.13-2.74), p=0.01

Mohan et al., JASN 2012
Tools used for preventing and treating AMR

- **Apheresis for antibody depletion**
  - Plasmapheresis
  - Immunoadsorption

- **Modulation of adaptive or innate immunity**
  - IVIG
  - Rituximab
  - ATG
  - Bortezomib
  - Eculizumab
  - Splenectomy
Desensitization

Before Transplantation

Living donors

At Transplantation

Deceased donors
Immunological risk assessment

Desensitization
IVIg
High dose IVIg

- Pilot study: 13 patients: 11 DD and 2 LD (PRA ≥50%)
- Pre-transplant: IVIg 2g/kg / 4 weeks. 3 courses
- Post-transplant: IVIg 2g/kg at days 0 & 1, 20 & 21, 40 & 41.
- IS : ATG, Tacrolimus, MMF, steroids,

Median follow-up > 12 months
Graft loss: 2 /13

Glotz et al., AJT 2002
**IVIg High doses (NIH IG02 trial)**

- Prospective randomized trial: 98 patients (DD & LD): 48 IVIg and 50 Placebo
- PRA > 80%
- IVIg 2g/kg 1/month for 4 months, then month 12 and month 24
- Follow-up to month 30

**Shorter time to transplantation**

<table>
<thead>
<tr>
<th></th>
<th>IVIg n=16</th>
<th>Placebo n=8</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft loss</td>
<td>25%</td>
<td>38%</td>
<td>ns</td>
</tr>
<tr>
<td>2-yr graft survival</td>
<td>80%</td>
<td>75%</td>
<td>ns</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>59%</td>
<td>10%</td>
<td>0.04</td>
</tr>
<tr>
<td>2y serum creatinine (mg/dL)</td>
<td>1.68 +/- 0.28</td>
<td>1.28 +/- 0.13</td>
<td>ns</td>
</tr>
</tbody>
</table>

P<0.05
IVIg: transient or no effect on PRA and cPRA

- 27 kidney transplant candidates with cPRA at 100%
- IVIg (2 g/kg) monthly for 4 months

Jordan et al., JASN 2004

Alachkar et al., Transplantation 2012
**Plasmapheresis and IVIg in LD Kidney-transplantation**

- 211 patients: CDC XM+ and/or FCXM + and /or DSA +
- Goal: CDC XM (−) before transplantation
- PP (minimum: 2) + 100 mg/kg anti-CMV Ig
- RATG or anti-IL2R/ Tac/MMF/Cs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 211)</th>
<th>Positive Results on Cross-Matching Assay†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CDC (N = 74)</td>
</tr>
<tr>
<td>Calculated panel-reactive antibody (%)</td>
<td>82±23</td>
<td>90±15</td>
</tr>
<tr>
<td>Donor-specific anti-HLA antibody (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA class I</td>
<td>41.2</td>
<td>33.8</td>
</tr>
<tr>
<td>HLA class II</td>
<td>25.6</td>
<td>24.3</td>
</tr>
<tr>
<td>HLA class I and II</td>
<td>33.1</td>
<td>41.9</td>
</tr>
<tr>
<td>Plasmapheresis sessions (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before transplantation</td>
<td>4±4</td>
<td>6±5</td>
</tr>
<tr>
<td>After transplantation</td>
<td>5±4</td>
<td>8±6</td>
</tr>
</tbody>
</table>
Plasmapheresis and IVIg: Outcome

Montgomery et al., N Engl J Med 2011
Plasmapheresis and IVIg: graft survival and acute rejection

- 129 HLAi KTx patients: desensitization PP (alternate days) + IVIg (100 mg/kg)
- 745 kidney biopsies
- Protocol biopsies: 1, 3, 6 and 12 months + indication biopsies
- Graft survival: 98% at 1 year and 80% at 5 year
- Acute rejection: 70% of patients

Bagnasco et al., Transplantation 2013
Plasmapheresis and IVIg: Graft histology

A

N of patients

0 20 40 60 80 100 120 140

1 3 6 12

Protocol bx

All bx

Months post transplant

All biopsies

Protocol

188
85
139
92
158
99
172
101

B

TxGN

P < 0.0001

cg score

0 1 2 3 4 5 6

3 6 12 24 36 48

N biopsies

Total

327 158 172 26 53 16

P < 0.0001

IF/TA

P < 0.0001

N biopsies

Total

327 158 172 26 53 16

Bagnasco et al., Transplantation 2013
IVIg + Rituximab
Plasmapheresis /IVIg/ Rituximab in LD Kidney-transplantation

- 28 patients: T CDC XM+ and/or B CDC XM+ and DSA +
- Goal: CDC XM (−) before transplantation
- PP [ before: 5.5 (1-15) and after KT]
- IVIg (10g x 3 /week)
- Rituximab (375 mg/m², 1 or 2 before KT, n=21)
- RATG (n=9) or anti-IL2R (n=18)/ Tac/MMF/Cs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>42%</td>
</tr>
<tr>
<td>AMR</td>
<td>39%</td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>1.5 (0.5-3.3)</td>
</tr>
</tbody>
</table>

Graft survival: 85%

**FIGURE 1.** Kaplan-Meier plot of renal allograft survival.

Magee et al., Transplantation 2008
IVIg + Rituximab

- IVIg: 2g/kg days 1 and 30
- Rituximab 1g at day 15 (initially: 1 g at days 7 and 22)
- Induction: Alemtuzumab or Daclizumab or RATG
- Tac/MMF/Cs

- Sensitized patients: High PRA, Positive CDC XM, Positive FCXM, DSA +
- 146 patients: 45 LD and 101 DD
- Mean time between desensitization and KT for DD \( \approx 5 \) months

- An acceptable crossmatch: negative CDC at least at a 1:2 dilution of sera.
- Acceptable DSAs: SA class I < 5000 MFI and positive FCXM-T< 225 MCS.
- Acceptable B-cell FCXM < 250 MCS and SA DSA > 10, 000 MFI

Vo et al., NEJM 2008
Vo et al., Transplantation 2010
Vo et al., Transplantation 2013
IVIg + Rituximab: Immunological outcome

Vo et al., Transplantation 2010
IVIg + Rituximab: Clinical outcome

### 48 months patient survival

- **100% Living Donor**

### 48 months death censored graft survival

- **95% Living Donor**
- **87.5% Deceased Donor**

- **Mean Follow-up:** 30 ± 17 months
- **Acute rejection rate:** 29% (21% AMR and 8% TCMR)
- **Death-censored graft loss:** 8%
- **Mean creatinine level at 3-years:** 115 µmol/L.

**Vo et al., Transplantation 2013**
Limited efficacy of IVIg + Rituximab: Rebound

- 31 KTx candidates
- PRA ≥50%
- IVIg (2g/kg) days 0 and 30
- Rituximab 1g at day 15

Lobashevsky et al., Transplantation 2013

23/24 (96%)

24/26 (92%)
2006 → 2012: 226 highly sensitized patients received transplants after desensitization.

• **Desensitization:**
  
  - IVIg (2 g/kg D1 & D30)
  
  - Rituximab (1 g D15)

• **IS:** Alemtuzumab (Tac / MPA / Cs)

  → 181 (80%) had no antibody-mediated rejection

  45 (20%) had antibody-mediated rejection
Factors predicting risk for antibody-mediated rejection and graft loss in highly human leukocyte antigen sensitized patients transplanted after desensitization (2)

Characteristics of ABMR in patients with or without graft loss

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No graft loss (n=27)</th>
<th>Graft loss (n=18)</th>
<th>( ^a P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4d(^+)/C4d(^-)</td>
<td>17 (63%) /10 (37%)</td>
<td>16 (89%) /2 (11%)</td>
<td>0.086</td>
</tr>
<tr>
<td>TMA(^+)</td>
<td>2(7%)</td>
<td>6 (33%)</td>
<td>0.045</td>
</tr>
<tr>
<td>TMA(^+)/Eculizumab(^+)</td>
<td>2/2 (100%)</td>
<td>0/6 (0%)</td>
<td>0.036</td>
</tr>
<tr>
<td>DSA RIS(^b) at Transplant</td>
<td>19.9 ±17</td>
<td>22±17</td>
<td>0.43</td>
</tr>
<tr>
<td>DSA RIS(^b) at ABMR</td>
<td>14.5±11.5</td>
<td>16.6+12.1</td>
<td>0.75</td>
</tr>
<tr>
<td>DSA RIS(^b) 1M post-ABMR(^c)</td>
<td>10.1±6.5</td>
<td>9.7+8.1</td>
<td>0.87</td>
</tr>
</tbody>
</table>

\( ^a \) P value was based on the Fisher exact test for C4d\(^+\)/C4d\(^-\) and TMA\(^+\)/TMA\(^+\)/Eculizumab\(^+\); P value for DSA-RIS was based on Mann-Whitney or Wilcoxon rank sum test.

\( ^b \) RIS [0 points = No DSA; 2 points = <5,000 MFI; 5 points = 5,000-10,000 MFI; 10 points = >10,000 MFI].

\( ^c \) DSA-RIS at ABMR vs. DSA-RIS at 1 month post-ABMR treatment: \( P=0.75 \) no graft loss and \( P=0.87 \) for graft loss.

TMA, thrombotic microangiopathy; DSA, donor-specific antibody; RIS, relative intensity scale; RIS, relative intensity scale; MFI, mean fluorescent intensity; ABMR, antibody-mediated rejection.
Factors predicting risk for antibody-mediated rejection and graft loss in highly human leukocyte antigen sensitized patients transplanted after desensitization (3)

Death censored graft survival by ABMR status

This figure shows death censored graft survival by ABMR status. A significant survival benefit was associated with freedom from ABMR.
Lack of effect in desensitization with IVIg and rituximab in highly sensitized patients

11 highly sensitized (cPRA >50%) desensitized with IVIg 2 g/kg D0 and D30) + rituximab 375 mg/m² D15.

A, Number of unacceptable antigens (UA) removed after desensitization. B, Average mean fluorescence intensity (MFI) values of class I UA before and after desensitization. C, Average MFI values of class II UA before and after desensitization.
High IVIg vs. PP/Rituximab/IVIg in DD Kidney-transplantation

Group I: Only IVIg (n=36)

Group II: IVIg + PP + Rituximab (n=18)
<table>
<thead>
<tr>
<th></th>
<th>IVIg n= 36</th>
<th>PP/R/IVIg n=18</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft loss</td>
<td>11.1%</td>
<td>11.1%</td>
<td>ns</td>
</tr>
<tr>
<td>1-yr GFR</td>
<td>43.1±16.2</td>
<td>53.8±15.6</td>
<td>0.04</td>
</tr>
<tr>
<td>1-yr proteinuria</td>
<td>0.3±0.34</td>
<td>0.1±0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>AAMR</td>
<td>19.6%</td>
<td>16.6%</td>
<td>ns</td>
</tr>
<tr>
<td>1-yr ptc</td>
<td>1.6±0.2</td>
<td>1.0±0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>1-yr cg</td>
<td>0.4±0.1</td>
<td>0.07±0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>CAMR</td>
<td>41.3%</td>
<td>13.3%</td>
<td>0.03</td>
</tr>
<tr>
<td>Subclinical AMR</td>
<td>44.8%</td>
<td>7.1%</td>
<td>0.02</td>
</tr>
</tbody>
</table>
*Immunoadsorption (IA)*
Immunoadsorption in DD Kidney-transplantation

- IA with staphylococcal protein A column: Before KT and after KT
- Polyclonal antibodies (90%)/ Anti-IL2R (10)
- Tac or CsA/MMF or AZA/Cs

- Objective: Positive CDC XM → Negative CDC XM
- 14 CDC XM remained positive (no difference in type and MFI of DSAs)

<table>
<thead>
<tr>
<th>Variables</th>
<th>CDCXM+/DSA+ (N = 21)</th>
<th>CDCXM-/DSA+ (N = 30)</th>
<th>CDCXM-/DSA- (N = 17)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%CDC-PRA, median (IQR)</td>
<td>82 (62–94)</td>
<td>73 (51–92)</td>
<td>68 (51–78)</td>
<td>0.10</td>
</tr>
<tr>
<td>HLA mismatch (A, B and DR), median (IQR)</td>
<td>3 (2–4)</td>
<td>3 (2–3)</td>
<td>3 (1–4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Cold ischemia time (h), median (IQR)</td>
<td>18 (14–22)</td>
<td>17 (12–22)</td>
<td>17 (15–22)</td>
<td>0.90</td>
</tr>
<tr>
<td>Peritransplant IA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate pretransplant IA session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processed plasma volume (L), median (IQR)</td>
<td>9 (7–11)</td>
<td>8 (7–9)</td>
<td>8 (8–11)</td>
<td>0.57</td>
</tr>
<tr>
<td>Duration of treatment (h), median (IQR)</td>
<td>5 (4–7)</td>
<td>5 (4–6)</td>
<td>4 (4–7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Posttransplant IA treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of IA sessions, median (IQR)</td>
<td>8 (5–11)</td>
<td>10 (7–13)</td>
<td>10 (6–13)</td>
<td>0.21</td>
</tr>
<tr>
<td>Duration of treatment course (days), median (IQR)</td>
<td>13 (6–24)</td>
<td>22 (14–27)</td>
<td>17 (12–33)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

- DSA type similar in both groups
- Anti-class II DSA MFI was higher in patients with CDCXM+
IA in DD Kidney-transplantation: Outcome

<table>
<thead>
<tr>
<th>XM+/DSA+ (n=21)</th>
<th>XM-/DSA+ (n=30)</th>
<th>XM-/DSA- (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 14%</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>AAMR 19%</td>
<td>23%</td>
<td>24%</td>
</tr>
<tr>
<td>CAMR 5%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>DGF 38%</td>
<td>47%</td>
<td>47%</td>
</tr>
<tr>
<td>5-yrs creat 1.3 mg/dL</td>
<td>1.8 mg/dL</td>
<td>1.7 mg/dL</td>
</tr>
<tr>
<td>5-yrs Prot (g/L)</td>
<td>&lt;0.05</td>
<td>0.06 (0.05-0.27)</td>
</tr>
</tbody>
</table>

No difference between patients with or without AMR

Bartel et al., AJT 2010
23 patients: Living donation

Baseline XMs:  
- CDC XM + / DSA + (n=11)
- CDC XM - / ELISA XM + / DSA + (n=1)
- CDC XM - / ELISA XM - / DSA + (n=11)

Aims: CDC and ELISA XMs negative and DSA MFI < 1000

Morath et al., Transplant Int 2012
Klein et al., Atherosclerosis Supplements 2013
Two graft losses at days 750 and 810 days.

- 2-year graft survival (%): 100
- Actual serum creatinine (mg/dL) — median: 1.42 (0.78–2.50)
- Actual MDRD-GFR (mL/min/1.73 m²) — median (range): 59.5 (19.4–78.1)
- Actual urinary protein-to-creatinine ratio — median (range): 0.12 (0.06–1.56)
- Loss of luminex DSA at day 360 — N (%): 10 out of 14 (71)
  - De novo DSA: 1 (4)\(^a\)
  - Persistent DSA: 2 (9)
  - Reemerging DSA: 2 (9)\(^a\)
- Patients with at least one acute rejection episode — N (%)
  - Borderline changes: 18 (78)
  - Acute T-cell mediated rejection (≥Banff’ IA): 1 (4)
  - Acute antibody-mediated changes: 1 (4)
  - Mixed acute cellular and antibody-mediated rejection: 4 (17)

\(^a\) Significant difference (p < 0.05)
Toulouse experience

- We started in April 2011
- 23 KTx candidates:
  - 15 HLAi
  - 8 ABOi/HLAi

IA used semi-specific columns, i.e. Immunosorba or Globaffin
## Outcome

<table>
<thead>
<tr>
<th>ABOi / HLAi (n=8)</th>
<th>HLAi (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1 graft loss (renal vein thrombosis)</td>
<td>- 3 graft losses (2 recurrences of FSGS; 1 due to chronic humoral rejection)</td>
</tr>
<tr>
<td>- 2 acute humoral rejections</td>
<td>- Rejections:</td>
</tr>
<tr>
<td>- 1 chronic humoral rejection</td>
<td>• 2 thrombotic microangiopathy</td>
</tr>
<tr>
<td>- Serum creatinine at last follow-up: 120 (90-180) µmol/L</td>
<td>• 2 acute humoral rejections</td>
</tr>
<tr>
<td></td>
<td>• 1 acute cellular rejection</td>
</tr>
<tr>
<td></td>
<td>- Serum creatinine at last-follow-up: 130 (60-280) µmol/L</td>
</tr>
</tbody>
</table>
Others
Desensitization using Eculizumab (anti-C5a)

- Study group: Eculizumab/RATG/Tac/MMF/Cs
- Historical group: Plasmapheresis post-transplant/RATG/Tac/MMF/Cs
- 1 Pre-transplant plasmapheresis if mean channel shift \( \geq 300 \)

**Anti-C5 Treatment Protocol**

-weeks 0 1 2 3 4 5 6 7 8 9 11 13

- Doses (mg)
  - Weeks 0, 1, 2, 3, 4: 1,200
  - Weeks 5, 6, 7: 1,200
  - Weeks 8-13: 1,200 every 2 weeks

BFXM <200, stop
## Eculizumab in sensitized LD

<table>
<thead>
<tr>
<th>Category</th>
<th>Eculizumab group (n = 26)</th>
<th>Control group (n = 51)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (mean months ± SD, range)</td>
<td>11.8 ± 6.3 (3.0–27.5)</td>
<td>48.8 ± 14.1 (7.8–69.8)</td>
<td></td>
</tr>
<tr>
<td>Graft survival at 1 year (n, %)</td>
<td>16/16 (100%)</td>
<td>49/51 (96%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Antibody-mediated rejection ≤ 3 months (n, %)</td>
<td>2 (7.7%)</td>
<td>21 (41%)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Patients developing high DSA levels ≤ 3 months¹</td>
<td>13 (50%)</td>
<td>22 (43%)</td>
<td>0.63</td>
</tr>
<tr>
<td>High DSA biopsies C4d+ (n, %)</td>
<td>13 (100%)</td>
<td>20 (91%)</td>
<td>0.52</td>
</tr>
<tr>
<td>High DSA and C4d+ biopsies showing AMR (n, %)</td>
<td>2 (15%)</td>
<td>20 (100%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cellular rejection ≤3 months (n, %)</td>
<td>1 (6.2%)</td>
<td>1 (2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Plasma exchange posttransplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients receiving PE (n, %)</td>
<td>3 (12%)</td>
<td>39 (76%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of PE treatments (mean ± SD)</td>
<td>0.35 ± 1.1</td>
<td>7.9 ± 7.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Splenectomy (n, %)</td>
<td>0 (0%)</td>
<td>9 (18%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Graft dysfunction in first month (mg/dL)</td>
<td>0.45 ± 0.37</td>
<td>0.93 ± 1.15</td>
<td>0.05</td>
</tr>
<tr>
<td>maximum serum creatinine – nadir serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology at 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant glomerulopathy incidence (n, %)</td>
<td>1/15 (6.7%)</td>
<td>15/42 (36%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Cg score (mean ± SD)</td>
<td>0.20 ± 0.78</td>
<td>0.74 ± 1.13</td>
<td>0.17</td>
</tr>
<tr>
<td>Ci score (mean ± SD)</td>
<td>1.00 ± 0.76</td>
<td>0.79 ± 0.80</td>
<td>0.31</td>
</tr>
<tr>
<td>Ct score (mean ± SD)</td>
<td>1.13 ± 0.74</td>
<td>0.91 ± 0.80</td>
<td>0.33</td>
</tr>
<tr>
<td>Cv score (mean ± SD)</td>
<td>0.80 ± 0.68</td>
<td>0.59 ± 0.74</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Stegall et al., AJT 2011
Desensitization using Bortezomib

- Arm A: RATG (1.5 mg/kg POD 0, 2, 4, 6, 8, 10)
- Arm B: RATG (1.5 mg/kg POD 0, 2, 4, 6, 8) + Rituximab (375 mg/m² POD 1)
- Arm C: RATG (1.5 mg/kg POD 0, 2, 4, 6, 8) + Bortezomib (1.3 mg/m² POD 0, 3, 7, 10)
- Arm D: RATG (1.5 mg/kg POD 0, 2, 4, 6, 8) + Bortezomib (1.3 mg/m² POD 0, 3, 7, 10) + Rituximab (200 mg/m² POD 1)
- Tac/MMF/Cs in all arms

<table>
<thead>
<tr>
<th></th>
<th>rATG alone (N = 10)</th>
<th>rATG + Ritux (N = 10)</th>
<th>rATG + Bortez (N = 10)</th>
<th>rATG + Ritux + Bortez (N = 10)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall acute rejection, n (%)</td>
<td>2 (20%)</td>
<td>0 (0%)</td>
<td>5 (50%)</td>
<td>3 (30%)</td>
<td>0.084</td>
</tr>
<tr>
<td>Early acute rejection, n (%)</td>
<td>2 (20%)</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
<td>2 (20%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Late acute rejection, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
<td>1 (10%)</td>
<td>0.60</td>
</tr>
<tr>
<td>First rejection episode, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody-mediated rejection</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
<td>1 (10%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Acute cellular rejection</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mixed acute rejection</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Recurrent rejection, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Time to first rejection posttransplant (days), median (25th–75th percentile)</td>
<td>26.5 (7–46)</td>
<td>N/A</td>
<td>14 (10–276)</td>
<td>17 (7–293)</td>
<td>0.92</td>
</tr>
<tr>
<td>C4d positive biopsy at first rejection diagnosis, n (%)</td>
<td>1 (10%)</td>
<td>N/A</td>
<td>2 (20%)</td>
<td>3 (30%)</td>
<td>0.54</td>
</tr>
<tr>
<td>DSA present at first rejection diagnosis, n (%)</td>
<td>1 (10%)</td>
<td>N/A</td>
<td>4 (40%)</td>
<td>3 (30%)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

- Significantly more nausea/vomiting and more new onset or worsening peripheral neuropathy in patients receiving bortezomib

Ejaz et al., AJT 2013
Desensitization: for which recipient?

Living donor:
- No
- Paired Kidney donation chain

Deceased donor:
- No
- Organ Shortage
  - Worst results
- Yes
  - After risk stratification
    - Very few patients

Controversial issue
Limits for desensitization strategy

• Which patients?
  T CDC XM + ? B CDC XM + ? T FCXM + ? B FCXM +? DSA + ?

• Which Goal?
  T CDC XM - ? B CDC XM - ? DSA MFI < 1000 or < 3000 ?

• Whatever the type and MFI of the DSA?

• Long-term outcome, GFR, proteinuria, histology…..

• Who should be offered a desensitization protocol ? Public health problem.
In summary, which desensitization strategy?

IA/PP
+ Rituximab
+ IVIg

- Bortezomib and Eculizumab under investigation
Thank you for your attention.