Acute antibody-mediated rejection

Pr. Lionel ROSTAING
Departement of Nephrology and Transplantation
CHU Michallon, Grenoble, France
lrostaing@chu-grenoble.fr

2nd ICNU meeting Tehran August 1st 2016
Targets of acute rejection

- Kidney $\rightarrow$ tubular epithelium, endothelium (glomeruli, peritubular capillaries)
  - Prevalence of acute cellular rejection (ACR): 10 to 15%
  - Prevalence of acute humoral rejection (AMR): a few %

- What are the culprits in acute rejection?
  - ACR: Activated cytotoxic T cells (CD8$^+$, CD45 RO$^+$, DR$^+$, Perforin$^+$, granzyme B$^+$, Fas L$^+$)
  - AMR: Donor-specific alloantibodies; complement activation
Vascular/ humoral rejection

• It is mediated either by preformed DSA although present at a very low titer at pretransplant (negative CDC cross match) or by *de novo* DSA
  - Anti-HLA alloantibodies
  - Anti-endothelial cell antibodies
  - Mostly present in women (miscarriages, pregnancies), and in patients previously transfused

• Histology :
  - Vascular lesions (endarteritis; C4d deposits along the vascular walls)
    - Haemorraghic necrosis in the absence of treatment
    - **Less than 10% of overall acute rejection episodes unless patients are not screened at pretransplant by Luminex.**
Acute/active AMR; all three features must be present for diagnosis

1. Histologic evidence of acute tissue injury, including one or more of the following:
   - Microvascular inflammation ($g > 0$ and/or $ptc > 0$)
   - Intimal or transmural arteritis ($v > 0$)
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   - Linear C4d staining in peritubular capillaries ($C4d2$ or $C4d3$ by IF on frozen sections, or $C4d > 0$ by IHC on paraffin sections)
   - At least moderate microvascular inflammation ($[g + ptc] \geq 2$)
   - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated

3. Serologic evidence of donor-specific antibodies (DSAs) (HLA or other antigens)

Haas M et al. Am J Transplant 2014;14:272-283
Chronic, active AMR; all three features must be present for diagnosis

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
   - Transplant glomerulopathy (TG) (cg > 0), if no evidence of chronic thrombotic microangiopathy > 0
   - Severe peritubular capillary basement membrane multilayering (requires EM)
   - Arterial intimal fibrosis of new onset, excluding other causes

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥ 2)
   - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated

3. Serologic evidence of DSAs (HLA or other antigens)
Identification of four distinct rejection patterns according to clinical, histological, and immunological variables
The unsupervised principal component analysis examined kidney recipients with acute biopsy-proven rejection with seven variables: glomerulitis, peritubular capillaritis, donor-specific anti-HLA antibodies, C4d deposition, interstitial inflammation, tubulitis, and endarteritis. The horizontal axis opposes cellular rejection (interstitial inflammation and tubulitis) and antibody-mediated rejection (donor-specific anti-HLA antibodies, glomerulitis, peritubular capillaritis and C4d), as recognised by the international Banff classification. The vertical axis defines the presence or absence of lesions of endarteritis (appendix).
Antibody-mediated vascular rejection of kidney allografts: a population-based study (2)

Comparison of morphological and immunological variables in the four rejection patterns

Bars represent SD. NS=not significant.
- TCMR/V− = T cell-mediated rejection without vasculitis.
- TCMR/V+ = T cell-mediated vascular rejection.
- ABMR/V+ = antibody-mediated vascular rejection.
- ABMR/V− = antibody-mediated rejection without vasculitis.

Antibody-mediated vascular rejection of kidney allografts: a population-based study (3)

Kaplan-Meier curves for kidney graft survival by acute rejection phenotype
Initial diagnoses as per (A) Banff classifications and (B) our new approach. Graft survival in patients without rejection is purely illustrative; graft survival in these individuals starts at time of transplantation.

- TCMR/V− = T cell-mediated rejection without vasculitis.
- TCMR/V+ = T cell-mediated vascular rejection.
- ABMR/V− = antibody-mediated rejection without vasculitis.
- ABMR/V+ = antibody-mediated vascular rejection.
Multivariate analysis of factors associated with graft loss in patients with antibody-mediated vascular rejection.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Numbers of events</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intersitial inflammation and tubulitis score*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 3 )</td>
<td>32</td>
<td>7</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>( &gt;3 )</td>
<td>32</td>
<td>14</td>
<td>4.33 (1.5-12.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Endarteritis score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;3 )</td>
<td>52</td>
<td>15</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>(3 )</td>
<td>12</td>
<td>6</td>
<td>5.17 (1.8-14.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>DSA(_\text{max} ) MFI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;3000 )</td>
<td>41</td>
<td>9</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>(\geq 3000 )</td>
<td>23</td>
<td>12</td>
<td>3.88 (1.5-9.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Treatment strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids and intravenous immune globulin</td>
<td>13</td>
<td>7</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Steroids plus monomab-CD3 or rabbit antithymocyte globulin</td>
<td>29</td>
<td>11</td>
<td>0.4 (0.2-1.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Steroids, plasmapheresis, intravenous immune globulin, and rituximab</td>
<td>22</td>
<td>3</td>
<td>0.16 (0.04-0.66)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Hazard ratios were estimated in a single Cox proportional hazards model. DSA\(_\text{max} \) MFI=maximum mean intensity of fluorescence of donor-specific anti-HLA antibodies.

*Interstitial inflammation and tubulitis score was defined as the sum of interstitial inflammation and tubulitis, and was graded from 0 to 6.
The type of acute rejection does influence kidney allograft outcome

Impact of de novo DSA after kidney transplantation

- If DSA does appear at the time of acute rejection
  ➢ ↓ Allograft survival

- Rapid decrease in DSA following specific therapy
  → Improvement in allograft survival

Acute rejection with or without de novo DSA: impact upon kidney allograft survival
IgG Donor-Specific Anti-Human HLA Antibody Subclasses and Kidney Allograft Antibody-Mediated Injury (1)

Flow chart of the study population.

647 Kidney Transplant Recipients  
01/2008-12/2009

635 Recipients screened for DSA in the first year post-transplant

Recipients with DSA (N=125)

Excluded: Recipients with desensitization protocols (N=12)

Acute ABMR (N=51)

sABMR (N=36)

No ABMR (N=38)

- Circulating DSA characteristics: class, specificity, MFI
- DSA IgG subclasses
- C1q-binding DSA
- Allograft histology
Study period: 2008-2010 → 635 consecutive kidney transplantations: of these 125 had donor-specific alloantibodies (DSA) within the first year posttransplantation

- DSAs were studied: specificity; HLA class specificity; mean fluorescence intensity (MFI); C1-q binding; IgG subclasses; graft injury phenotype

Overall:
- 40.8% had acute antibody-mediated rejection (aABMR)
- 28.8% had subclinical ABMR
- 30.4% were ABMR-free

- The MFI of the immunodominant DSA (iDSA), i.e. the DSA with the highest MFI level was 6724 +/-464, and 41.6% of patients had iDSA showing C1q positivity.
- The distribution of iDSA IgG 1-4 subclasses among the population was 75.2%, 44%, 28%, and 26.4%.
IgG Donor-Specific Anti-Human HLA Antibody Subclasses and Kidney Allograft Antibody-Mediated Injury (3)

Distribution of IgG1–4 iDSA subclasses in the study population (Venn diagram).

N=21 without positive subclass
N=125 for the overall population

IgG1: N=31 (25%)
IgG1+2: N=14 (11%)
IgG1+2+3: N=13 (10%)
IgG1+2+3+4: N=9 (7%)
IgG1+2+4: N=17 (14%)

IgG1+3: N=8 (6%)
IgG1+4: N=2 (2%)
IgG2+4: N=2 (2%)
IgG3: N=5 (4%)
IgG4: N=3 (2%)
Identification of the three distinct rejection phenotypes according to the characteristics of the dominant donor-specific anti-HLA antibody (MFI, HLA class specificity, C1q-binding capacity, and IgG1–4).

Lefaucheur C et al. JASN 2015 August 2015
Kaplan–Meier curves for death-censored kidney allograft survival according to iDSA IgG1 (A), IgG2 (B), IgG3 (C), and IgG4 (D) subclass status.
Clinical and histologic characteristics according to the IgG3 status in the recipients with antibody-mediated injury (n=87)

<table>
<thead>
<tr>
<th></th>
<th>IgG3 positive n=35</th>
<th>IgG3 negative n=52</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to diagnosis* (d) – median (Q1–Q3)</td>
<td>35 (17–93)</td>
<td>356 (33–368)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR at biopsy (ml/min/1.73 m²) – mean ±SD</td>
<td>28.6±13.9</td>
<td>38.8±20.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Time to failure (d) – median (Q1–Q3)</td>
<td>628 (400–778)</td>
<td>1638 (1115–1692)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Histologic characteristics (Banff scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g + ptc score – mean±SD</td>
<td>3.9±1.3</td>
<td>3.0±1.1</td>
<td>0.002</td>
</tr>
<tr>
<td>i + t score – mean±SD</td>
<td>1.5±1.8</td>
<td>1.0±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>v score – mean±SD</td>
<td>0.5±0.9</td>
<td>0.3±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>cg score – mean±SD</td>
<td>0.4±0.9</td>
<td>0.4±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>IF/TA score – mean±SD</td>
<td>0.7±0.9</td>
<td>1.3±1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>cv score – mean±SD</td>
<td>1.2±1.0</td>
<td>1.5±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>C4d deposition – n (%)</td>
<td>28 (80.0)</td>
<td>19 (36.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Time between transplantation and allograft biopsy with concomitant anti-HLA antibodies assessment
Clinical and histologic characteristics according to the IgG4 status in the recipients with antibody-mediated injury (n=87)

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>IgG4 positive</th>
<th>IgG4 negative</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to diagnosis (d) – median (Q1–Q3)</td>
<td>365 (351–370)</td>
<td>33 (15–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR at biopsy (ml/min/1.73 m²) – mean±SD</td>
<td>46.7±19.0</td>
<td>27.4±14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to failure (d) – median (Q1–Q3)</td>
<td>1643 (1085–1673)</td>
<td>835 (628–1151)</td>
<td>NS</td>
</tr>
<tr>
<td>Histologic characteristics (Banff scores)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g + ptc score – mean±SD</td>
<td>3.2±1.2</td>
<td>3.5±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>i + t score – mean±SD</td>
<td>0.9±1.3</td>
<td>1.4±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>v score – mean±SD</td>
<td>0.2±0.6</td>
<td>0.5±1.0</td>
<td>0.08</td>
</tr>
<tr>
<td>cg score – mean±SD</td>
<td>0.7±0.9</td>
<td>0.1±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IF/TA score – mean±SD</td>
<td>1.5±0.9</td>
<td>0.7±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cv score – mean±SD</td>
<td>1.7±0.9</td>
<td>1.2±1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>C4d deposition – n (%)</td>
<td>11 (33.3)</td>
<td>36 (66.7)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Time between transplantation and allograft biopsy with concomitant anti-HLA antibodies assessment.
• Prospective cohort between 2000-2010 → 1307 consecutive kidney transplantations with CDC negative cross-match

• Prospective 1-year protocol kidney biopsies: at the same time assessments of DSA and C4d deposits.

  – Three groups of patients:

    • 727 (73%) pts without rejection

    • 132 (13%) with subclinical T cell-mediated rejection (TCMR)

    • 142 (14%) with subclinical antibody-mediated rejection (ABMR)
Distinct allograft injury phenotypes in 1 year screening kidney allograft biopsies. Graft injury phenotype in screening allograft biopsies performed at 1 year post-transplant (n=1001). Results are given as Banff scores for each lesion. Bars represent SEMs.
Distinct allograft injury phenotypes in 1 year screening kidney allograft biopsies. Graft injury phenotype in screening allograft biopsies performed at 1 year post-transplant (n=1001). Results are given as Banff scores for each lesion. Bars represent SEMs.
Identification of the three distinct rejection phenotypes according to the characteristics of the dominant donor-specific anti-HLA antibody (MFI, HLA class specificity, C1q-binding capacity, and IgG1–4).
Distinct kidney allograft function course according to the 1 year screening kidney allograft biopsies phenotype.

- Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts (5)

Loupy A et al. JASN 2015;26(7):1721-31
Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts (6)

Long-term allograft survival according to the one-year biopsy phenotype.

![Graph showing long-term allograft survival](image)

**Graph Description:**
- The graph illustrates the survival probability of grafts over time post-transplantation.
- Four categories are compared: No rejection (n=727), Subclinical TCMR (n=132), Subclinical ABMR (n=142), and No rejection (n=727).
- The logrank p-value is less than 0.0001, indicating a statistically significant difference in survival rates.

**Time post transplantation (years):**
- The x-axis represents time post transplantation in years, ranging from 0 to 8.
- The y-axis shows the graft survival probability.

**Graph Details:**
- Subclinical TCMR
- Subclinical ABMR
- No rejection

LOUPY A et al. JASN 2015;26(7):1721-31
Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts (7)

Long-term allograft survival according to the one-year biopsy phenotype.

Footnotes:
RR: Relative risk
GFR: Glomerular filtration rate estimated by the MDRD formula
95% CI values of the RR are 1.8 (0.2 - 15.6); 4.2 (2.2- 8.2); and 2.5 (1.1 - 5.3).
## Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts (8)

### Multivariate associations of clinical, functional, histologic, and immunologic parameters with kidney graft loss

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of Patients</th>
<th>Number of Events</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR at 1 yr, ml/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR ≥ 60</td>
<td>305</td>
<td>6</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>30 ≤ eGFR &lt; 60</td>
<td>577</td>
<td>38</td>
<td>2.86</td>
<td>1.21 to 6.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR &lt; 30</td>
<td>79</td>
<td>28</td>
<td>11.42</td>
<td>4.55 to 28.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Subclinical ABMR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>825</td>
<td>45</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>136</td>
<td>27</td>
<td>2.99</td>
<td>1.81 to 4.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Proteinuria at 1 yr (log&lt;sub&gt;10&lt;/sub&gt; value)</strong></td>
<td>961</td>
<td>72</td>
<td>1.50</td>
<td>1.26 to 1.79</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Final multivariate Cox model obtained by entering risk factors from the univariate model reaching P≤0.10 as the threshold in a single multivariate proportional hazards model. The final multivariate model is adjusted on the following parameters: (1) donor age, (2) donor type, (3) cold ischemia time, (4) graft rank, (5) delayed graft function, (6) atrophy scarring, and (7) C4d graft deposition. eGFR was estimated by the Modification of Diet in Renal Disease formula.
Acute AMR : yes, we have therapies
Chronic AMR : what can we do?

DSA and antibody-mediated rejection : treatment
AAMR: treatment by plasmapheresis alone (PP) or plasmapheresis + IVIg

Retrospective monocentric study: 13 AMR treated by PP alone (5)
Or by PP (5) + IVIg (0.5g/kg)

Retrospective, monocentric study (Saint-Louis Hospital, Paris) including 24 KTx patients with AMR and DSA:

- from 2000 to 2003 12 patients: IVIg 2g/kg within 2 days every 3 weeks x 4
- from 2004 to 2005 12 patients: (1 PP/d+IVIg 100mg/kg) x 4, then IVIg 2g/kg within 2 days every 3 weeks x 4 plus 2 rituximab infusions (375 mg/m²)

DSAs: outcome of maximal MFI between D0 and month 3 post-AMR treatment

DSAs: variation of $\Delta \text{max MFI}$ between D0 and month 3 post-AMR treatment

AAMR treatment: graft survival according to strategies

- Group A (n=12)
- Group B (n=12)

**PP/IVIg/Rituximab**

**IVIg**

- n=11
- n=6

p=0.02

AAMR treatment after KTx : place of Rituximab in addition to PP(+- IVIg)
# RITUX-ERAH: A prospective study

40 kidney-transplant-patients experiencing AMR

<table>
<thead>
<tr>
<th>D 1-5</th>
<th>PP: D1-D5 at least 3, and then 3/week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVIG: 100 mg/kg/d after each PP, followed by 2 g/kg at day 5</td>
</tr>
<tr>
<td></td>
<td>Steroids: 500 mg x 3, and then 1 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td></td>
<td>MMF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D5</th>
<th>Ritux (375 mg/m²) [n = 19]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D12</th>
<th>Primary objective: Graft loss or improvement of kidney function &lt; 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;D12</td>
<td>± Ritux (375 mg/m²) [n = 8]</td>
</tr>
<tr>
<td></td>
<td>± Ritux (375 mg/m²) [n = 6]</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 19)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>46.7 (16.2)</td>
</tr>
<tr>
<td>PRA at transplantation, n (%)</td>
<td>9 (47.3)</td>
</tr>
<tr>
<td>Median time to AMR</td>
<td>74.0 (14.0; 178.0)</td>
</tr>
<tr>
<td>Median Creatinine level at AMR (µmol/L)</td>
<td>204.0 (167.0; 324.0)</td>
</tr>
<tr>
<td>Median MFI at AMR</td>
<td>5 538 (1 400; 9 800)</td>
</tr>
<tr>
<td>Patient survival (%)</td>
<td>100</td>
</tr>
<tr>
<td>Graft survival (%)</td>
<td>94.7</td>
</tr>
<tr>
<td>Primary objective at day 12 : graft loss or improvement of kidney function &lt; 30 %)</td>
<td>52.6 %</td>
</tr>
<tr>
<td>Creatinine level at 1 year (µmol/L)</td>
<td>197</td>
</tr>
<tr>
<td>Persistance of AMR signs at month 6 kidney biopsy (%)</td>
<td>31.3</td>
</tr>
</tbody>
</table>
RITUX-EРАH: A prospective study (3)

![Graph showing DSA MFI over time for Placebo and Rituximab groups.](image)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 15)</th>
<th>Rituximab (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFI &lt; 2 000 at M12</td>
<td>6 (40 %)</td>
<td>13 (76.5 %)</td>
</tr>
</tbody>
</table>

p < 0.04

Sautenet B. et al., Transplantation. 2015 Nov 9.
Eculizumab and kidney transplant
ECULIZUMAB

- Eculizumab: registered for Paroxysmal nocturnal hemoglobinuria (PNH); in development for prevention/treatment of AAMR
Eculizumab: humanized anti-C5 moAb
Eculizumab to treat resistant acute antibody mediated rejection

A. One 17-year-old male, highly sensitized who lost his first allograft because of chronic rejection:
   - Desensitization protocol before the 2nd kidney transplant (deceased donor) including IVIg, PP and rituximab
     - 1 month post-Ktx AAMR (anti-DQ5; MFI 20,000) resistant to MP pulses and 45 PP sessions
   - Eculizumab therapy for 1 year
     - Two year later renal function is normal
Treatment of thrombotic microangiopathy due to APS recurrence after KTtx

- 3 APS kidney allograft patients who have had posttransplant thrombotic microangiopathy (TMA) due to recurrence of APS, which was resistant to plasmapheresis

- Eculizumab therapy resulted in a rapid and dramatic improvement of TMA lesions within the allograft.
  - No TMA flares after withdrawal of eculizumab by post-op months 3, 4 and 12
  - At the time of TMA recurrence immunofluorescence staining of the kidney biopsy showed intense C5-9 and C4d depositions in the endothelial cell surfaces of the injured vessels; C5-9 localized with vessels exhibiting a high rate of apoptotic cells.
  - However, complement inhibition did not present the development of chronic vascular changes associated with APS
  - Eculizumab is able to treat the acute severe forms of recurrent TMA associated with APS, but does not prevent the APS-associated chronic changes

3 APS patients with living donor; of those 1 have had catastrophic APS (CAPS)

- 2 had in addition DSA (plasmapheresis sessions pretransplant)
- Eculizumab therapy (life-long, twice monthly at 1200 mg)
- Follow-up: 4 months to 4 years: excellent kidney allograft function.

**Question**: how long should eculizumab therapy be given? Can it be stopped?
B. Personal experience:

- In Toulouse, 2 adult highly sensitized patients with iterative kidney transplant (living donor) with DSAs > 10,000
  - Desensitization protocol with IVIg. Rituximab, immunoadsorption → CDC cross-match negative at transplantation.
  - Severe AAMR with TMA features by day 5 posttransplant
    - Resistant to MP pulses, PP sessions
  - Salvage by Eculizumab infusions (up to posttransplant month 3); follow-up 30 and 24 months → normal renal function.

Eculizumab to treat resistant acute antibody mediated rejection

Rostaing L et al. 2016
FUTURE?
Report of inefficacy of Eculizumab in 2 cases of severe antibody-mediated kidney allograft rejection

- One patient received curatively Eculizumab for AAMR (DSA+)
- The other patient developed AAMR (DSA+) while being treated with Eculizumab after a relapse of atypical HUS
  - No effect of Eculizumab: why??
    - In these 2 cases no deposit of C4d in the allograft biopsy
    - Absence of C1q-binding of DSAs
  - This suggests a complement-independent mechanism underlying the pathogenesis of these 2 cases of AAMR.

Burbach M et al. Transplantation, 2014
Currently approved to treat hereditary angioedema (inherited disorder with decreased C1-INH concentration)

Under investigation in order to block complement pathways in various settings:

- Prevention of primary graft dysfunction after lung transplantation: better outcome than with placebo (Sommer W. et al., Transplantation, 2014; Feb 25).
- Human C1-INH attenuates liver ischemia-reperfusion injury and promotes liver regeneration in a mouse model (Saidi RF et al, J Surg Res, 2014;187:660-6)
- Recombinant human C1-INH prevents AAMR in alloimmunized baboons (Tilloux et al, Kidney Int, 2010;78:452-9)