New insights into treatment of acute/chronic humoral rejection

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Prevention of (c)AMR is better than treatment

FIGURE 2. Graft survival during years 3 to 7 posttransplant according to dose reductions or withdrawal of CsA, tacrolimus, and MMF during the second posttransplant year, compared with patients continuing to receive an unchanged dose. All $P$ values less than 0.001 for reduction or withdrawal vs. continuation (log rank).

(c)AMR = (chronic) antibody-mediated rejection, Opelz, Transplantation 2008
Factors influencing (c)AMR

Pretransplant: 
- Prior transplant
- Blood transfusion
- Pregnancy
- Mechanical assist device (Heart)

Posttransplant: 
- Specificity, strength (MFI/titer), ability to bind complement, isotype/subclass, density, affinity, and glycosylation

Pathology: 
- Dysfunction
- EC swelling
- Microvascular inflammation
- Macrophage infiltrate
- Complement deposition

Outcomes:
1. Stable function:
   - DSA+
   - IgG2, IgG4
   - C1q−, C4d−
2. Subclinical AMR:
   - DSA+
   - IgG2, IgG4
   - C1q−, C4d±
3. Clinical dysfunction:
   - Acute AMR
     - DSA+
     - IgG3, IgG1
     - C1q+, C4d+
   - Chronic AMR
     - DSA+
     - IgG2, IgG4
     - C1q+, C4d±

IgG subclasses and clinical outcomes

Acute AMR (AKARIS trial)

2001-2005: early (< 3 months) C4d-positive graft dysfunction
Tacrolimus conversion plus 9-14 immunoadsorptions

Table 2: Treatment following patient randomization and kidney allograft outcome

<table>
<thead>
<tr>
<th>Patient number</th>
<th>IA after index Bx</th>
<th>IA rescue</th>
<th>‘Anti-cellular’ treatment</th>
<th>Allograft function/serum creatinine (mg/dL) after randomization</th>
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<td>Index Bx</td>
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<td>-</td>
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<tr>
<td>4</td>
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<td>-</td>
<td>ATG</td>
<td>Dialysis</td>
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<td>Group B</td>
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<td>Dialysis</td>
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</table>

ATG = anti thymocyte globulin; IA = immunoadsorption.

1 Patient No. 7 died with functioning allograft because of aspiration pneumonia 5 weeks after randomization; 2 Beyond patient follow-up; 3 IA rescue was not performed because of early graft necrosis.
Figure 1: Kaplan–Meier kidney allograft survival [patient death (Group A) included] following randomization (Group A: solid line; Group B: dashed line). The Mantel–Cox log-rank test was used to compare graft survival between groups.
Outcomes of chronic-active AMR

Fig. 3. Kidney graft survival following cAMR diagnosis.

N=123 (Wisconsin, 2006-2012)
Median survival 1.9 years

Redfield, Hum Immunol 2016
Treatment of patients

Fig. 2. Treatment modalities.

IVIG = intravenous immunoglobulin; PLEX = plasma exchange; Ritux = Rituximab (anti-CD20); Thymo = Thymoglobulin
Response to treatment

**Fig. 5.** Kidney graft survival with IVIG/steroids following cAMR diagnosis.

Redfield, Hum Immunol 2016
Responsiveness related to cg and cv grades

IVIg

**IVIg**

**DSA course**

-61%

-63%

N = 20, four weekly doses of IVIg (1 g/kg body weight per dose), followed by a single dose of rituximab (375 mg/m² body surface area) 1 week after the last IVIg infusion

IVIg = intravenous immunoglobulins, Billing, Transplant Int 2012
Bortezomib versus Rituximab?

**Figure 1:** Graft survival according to Kaplan-Meier. Differences between groups were calculated by log-rank test. Note: none of the patients died with a functioning allograft. Group RLP, rituximab + low-dose IVIG + plasmapheresis; group BLP, bortezomib + low-dose IVIG + plasmapheresis; group BHP, bortezomib + high-dose IVIG + plasmapheresis. “+”, end of follow-up.

**Figure 2:** Serum creatinine before, during, and after treatment of antibody-mediated rejection of all patients with a functioning graft at each time point. Differences between groups were calculated by Kruskal-Wallis test with Dunn-Bonferroni post hoc test. Group RLP, rituximab + low-dose IVIG + plasmapheresis; group BLP, bortezomib + low-dose IVIG + plasmapheresis; group BHP, bortezomib + high-dose IVIG + plasmapheresis. *p = 0.02 versus group RLP and group BLP.
Complement-C5 inhibition

Living donor kidney transplantation, pos. FCXM, N = 26
Plasmapheresis at > 300 channel shifts
Acute AMR at 3 months 8% versus 41% in controls

Anti-C5 Treatment Protocol

FCXM = flow-cytometry crossmatch, Stegall, Am J Transplant 2011
Complement-C5 inhibition

Living donor kidney transplantation, pos. FCXM, N = 30
Plasmapheresis at > 300 channel shifts, minimum 2 years of follow-up
Acute AMR 7% versus 44% in controls

FCXM = flow-cytometry crossmatch, Cornell, Am J Transplant 2015
Complement-C5 inhibition

N = 15 with deteriorating kidney function, AMR (50% C4d+) and DSA (50% C1q+)
Eculizumab 6 m, observation 6 m (N = 10) compared to observation only (N = 5)

Positive effect on:
eGFR
C1q-DSA

No effect on:
DSA-MFI
Morphology
ENDAT expression

Figure 3: Mixed model analysis of eGFR slope comparing study arms during the first 6 mo. Analysis used eGFR, group, time, and group-by-time variables. Treated participants showed stabilization of renal function at the a priori 0.1 significance level (p = 0.09). eGFR, estimated GFR.
Complement-C1 inhibition

Phase-2b trial, N = 9 C1 INH in patients with AMR (in addition to SOC)
Total of 20,000 units C1 INH every other day for two weeks
Primary end-point: 20-day pathology compared to SOC (N = 9)

Positive effect on:
- GFR (trend)
- 6m TG (trend)

No Effect on:
- Morphology
- Graft survival

SOC = standard of care, TG = transplant glomerulopathy, Montgomery, Am J Transplant 2016
Anti–IL-6 receptor ab tocilizumab

N = 36 with cAMR, TG and DSA who failed standard of care

Tocilizumab monthly infusions (8 mg/kg b.w.), 9 patients with 1-year repeat biopsy

80% 6-year graft survival

Ab = antibody, TG = transplant glomerulopathy, Choi, Am J Transplant 2017
Conclusions

• > 50% of graft loss due to cAMR
• Risk factors!
• Prevention of DSA-development!
• Therapy of early AMR lesions feasible
• Chronic lesions – no effective therapy
• HD: aAMR: immunoadsorption/plasmapheresis, cAMR: IVIg/Rituximab (plus immunoadsorption when high DSA-MFI, C1q-DSA, active lesions)