Update on Transplant Glomerulopathy

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Disclosure

• Merck Co, Abbvie – Advisory Board
What is your diagnosis?

• 56 yo Caucasian male with PMH significant for ESRD secondary to IgA NP received Tx from:
  • Low IR (no DSA), deceased donor (KDPI: 35-SCD), uneventful peri-operative period, received Thymo, on Tac-MMF-pred. D/C creatinine 110 micromol/l, no urine protein
  • 36 months post-Tx, new DSA (class II), 5 g/24h proteinuria, creatinine: 150 micromol/l
  • Biopsy shows:
Objectives

• Epidemiology of TG secondary to cABMR
• Pathology of TG secondary to cABMR
• Pathophysiology of TG secondary to cABMR
• Clinical and Immunological risk factors of TG secondary to cABMR
• Prevention of TG secondary to cABMR
• Treatment of TG secondary to cABMR
Objectives

- Epidemiology of TG secondary to cABMR
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Prevalence

• The prevalence of TG secondary to cABMR is poorly described in the literature.

• Analysis of one Italian center’s 666 graft biopsies data (collected between 1983-2000), demonstrated **TG in 5.6%** (Banfi G. et al., Transplantation, 2005)

• A higher **incidence (12%)** was reported from the Mayo Clinic group during 4.5 years of follow-up (Issa N. et al., Transplantation, 2008)

• The same group reported in a 582 patient cohort, a cumulative incidence of **20% at 5 years** in patients with negative pre-transplant T-cell complement dependent cytotoxicity cross-match (CDCXM) compared to **54.5% in a different desensitized positive CDCXM cohort** (Gloor JM et al., AJT, 2007 and Bentall A., AJT, 2013)
cABMR effects on outcome using Banff - 2013

- Large single center retrospective review using the updated BANFF 2013 criteria.
- 123 consecutive patients with biopsy proven cABMR (BANFF 2013) between 2006 and 2012.
- Patients identified with cABMR were followed for a median of 9.5 (2.7–20.3) years after transplant and 4.3 (0–8.8) years after cABMR.
- Ninety-four (76%) recipients lost their grafts with a median survival of 1.9 years after diagnosis with cABMR.
- Chronicity score >8 (HR 2.9, 95% CI 1–8.4, p = 0.05), DSA >2500 MFI (HR 2.8, 95% CI 1.1–6.8, p = 0.03), Scr >3 mg/dL (HR 3.2, 95% CI 1.6–6.3, p = 0.001) and UPC >1 g/g (HR 2.5, 95% CI 1.4–4.5, p = 0.003) were associated with a higher risk of graft loss.

cABMR effects on outcome using Banff - 2013

Fig. 3. Kidney graft survival following cAMR diagnosis.

At 4 years after cABMR only 25%

DSA has impact even without ABMR

• 1539 patients from 2 centers from France.
• 2260 per indication biopsies.
• 32% severe IF/TA (Banff grade 2 or more).
• HLA-DSAs were significantly associated with severe IF/TA (adjusted odds ratio, 1.53; 95% confidence interval 1.16–2.01).
• HLA-DSAs remained significantly associated with severe IF/TA in patients without antibody-mediated rejection (adjusted odds ratio 1.54; 1.11–2.14).

Gosset C. et al., KI, 2017
DSA has impact even without ABMR

Figure 6 | Kaplan-Meier estimates for death-censored kidney allograft survival according to 1-year posttransplantation interstitial fibrosis and tubular atrophy (IF/TA) severity and anti-human leukocyte antigen donor-specific antibody (DSA) status \( (n = 1539) \). w/o, without.
Can the outcome predicted?

• 92 patients in the developmental cohort
• 47 patients in the validation, external cohort
• 50% treated with steroid, IVIG, PEX, Thymo, Rituxomab, Bortezomib
• 70% developed graft failure in the follow-up period (60 months)
• Median time between Dx and Graft loss: 9 months

Patri P. et al., KI, 2016
Can the outcome predicted?

**Figure 5 | Kaplan-Meier analysis-estimated probability of allograft survival in an independent external cohort.** We used the same prognostic index cut-off values to define the three risk groups in an independent external cohort of 47 kidney allograft recipients with transplant glomerulopathy. The median allograft survival was 47 months from the diagnosis for the low-risk group, 19 months for the medium-risk group, and 1.6 months for the high-risk group. The hazard ratios for allograft failure were 2.18 (0.94–5.02) and 16.27 (4.62–57.28) for the medium- and high-risk groups, respectively, compared with the low-risk group. Table depicts the estimated allograft survival at various time points after the diagnosis. PI, prognostic index.
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Banff 2017 classification, the biopsy diagnosis of caABMR should meet three criteria:

Morphologic evidence of chronic tissue injury, including 1 or more of the following:
• 1. Transplant glomerulopathy (cg > 0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
• 2. Severe peritubular capillary basement membrane multilayering (requires EM)
• 3. Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required

Serologic evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:
• Linear or diffuse 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) in the absence of recurrent/de novo glomerulonephritis, includes changes evident by C4d staining or expression of validated transcripts/classifiers as noted above, in criterion 2 may substitute for DSA; however thorough DSA testing is strongly advised
• Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated

Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:
• Serologic evidence of donor-specific antibodies (DSA to HLA or transplant glomerulopathy (cg > 0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis, includes changes evident by electron microscopy (EM) alone (cg1a)
• C4d staining or expression of validated transcripts/classifiers as noted above, in criterion 2 may substitute for DSA; however thorough DSA testing is strongly advised

Haas M et al., AJT, 2018
Light microscopy revealed leukocyte accumulation (arrowheads) in the glomerular and peritubular capillaries (glomerulitis and peritubular capillaritis, respectively); double contoured glomerular capillary walls were not observed (HE stain; original magnification, x 400).

Immunofluorescence demonstrated C4d positivity in peritubular capillaries (C4d stain; frozen section, original magnification, x 200).

Electron microscopy of glomerular capillaries revealed subendothelial widening, focal loss of endothelial cell fenestrations, and the duplication of glomerular basement membrane along the entire capillary circumference (arrowhead) in three loops.

Well-developed transplant glomerulopathy is characterized histologically by widespread double contours of capillary loops (arrowheads). Asterisks indicate segmental sclerosis.
Differential diagnosis (diseases lead to GBM duplication):

- membranoproliferative glomerulonephritis,
- lupus glomerulonephritis,
- HCV virus infection-related glomerulonephritis,
- smoldering thrombotic microangiopathy (Hemolytic-uremic syndrome or anti-phospholipid antibody-induced – Cd4 NEGATIVE!)
Table 1 | Pathological features of patients with TG according to HCV and C4d status

<table>
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<tr>
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<th>n=16; %</th>
<th>HCV+ TG (n=9; %)</th>
<th>C4d+ TG (n=13)</th>
<th>C4d+TG (n=12)</th>
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<td>(69%)</td>
<td>(62%)</td>
<td>(42%)</td>
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<td>(71%)</td>
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<td>(63%)</td>
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Table 3 | Multivariate analysis of clinicopathological factors and time to graft loss

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<tr>
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<th>Likelihood ratio (P-value) based on proportional hazards (Cox fit)</th>
<th>Likelihood ratio (P-value) based on parametric survival fit</th>
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<tr>
<td>C4d</td>
<td>0.82 (P=0.36)</td>
<td>1.86 (P=0.17)</td>
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<td>TMA</td>
<td>0.14 (P=0.71)</td>
<td>0.29 (P=0.59)</td>
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<tr>
<td>HCV</td>
<td>4.56 (P=0.03)</td>
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Abbreviations: HCV, hepatitis C virus; TMA, thrombotic microangiopathy.

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<th>n=16</th>
<th>HCV+ TG (n=9)</th>
<th>P-value</th>
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<tr>
<td></td>
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<td>(median 3.4)</td>
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<td>117</td>
<td>61.0 ± 46.2</td>
<td>0.07</td>
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<td>1.1</td>
<td>2.3 ± 2.3</td>
<td>0.73</td>
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<tr>
<td></td>
<td>0%</td>
<td>9 (100%)</td>
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<td></td>
<td>34.9</td>
<td>10.1 ± 15.8</td>
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<td>120.5</td>
<td>71.1 ± 52.7</td>
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Figure 2 | Kaplan–Meier curves showing time to graft loss after transplantation in HCV+ TG and HCV− TG patients. HCV+ TG patients had a significantly faster progression to graft failure after Tx as compared with HCV− TG patients. HCV, hepatitis C virus; TG, transplant glomerulopathy; Tx, transplantation.
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Common pathway in pathophysiology

**Figure 2.** A schematic representation of the working proposal of evidence-based etiopathogenesis of transplant glomerulopathy. Abbreviations: HCV, hepatitis C virus infection; NK, natural killer cells; TMA, thrombotic microangiopathy.

Husain S and Sis B, AJKD, 2013
Pathophysiology

• Recurrent alloantibody-mediated (HLA antigen or non-HLA antigen) endothelial injury
• This induces different intracellular signaling leading to endothelial activation, recruitment of natural killer (NK) cells, monocytes and lesser T-lymphocytes and neutrophil granulocytes
• Non-HLA antigens: MHC Class I-related chain A (MICA), angiotensin II receptor type 1 activating autoantibody (AT1R Ab), anti-endothelial cell antibodies (EACAs)

Remport A et al., NDT, 2015
Pathophysiology of TG secondary to cABMR

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Clinical and Immunological risk factors of TG secondary to cABMR

- Medication non adherence
- Inappropriate reduction of ISU
- Pre-transplant/pre-existing high titer donor specific IgG anti-HLA antibodies
- De novo appearance of donor-specific IgG HLA antibodies (dnDSA)
- Non-HLA antibodies
- ABO incompatible renal transplantation

Remport A et al., NDT, 2015
TABLE 2. Baseline patient characteristics

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<th>Group</th>
<th>Number at Risk</th>
<th>Time (days)</th>
<th>Cumulative Rejection (%)</th>
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<td>25</td>
<td>10, 18</td>
<td>23, 14</td>
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<tr>
<td>dnDSA&gt;3000</td>
<td>23</td>
<td>10, 18</td>
<td>23, 14</td>
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**FIGURE 1.** Impact of the MFI level of the dnDSA on the risk of rejection. A, The group with an MFI greater than or equal to 3,000 has a higher risk for all rejection (cellular or antibody mediated) (HR, 8.61; 95% confidence interval, 2.67–27.8; log-rank \( P=0.0008 \)). B, the risk of AMR (includes AMR or mixed AMR-cellular rejection) was also higher for the group with MFI greater than or equal to 3,000 (HR, 10.6; 95% confidence interval, 2.27–49.5; log-rank \( P=0.006 \)). Numbers at the bottom of each figure represent the number of patients at risk at each time point. dnDSA, de novo donor-specific antibody; AMR, antibody-mediated rejection; MFI, mean fluorescence intensity; HR, hazard ratio.

Heilman RL et al., Transplantation, 2014
Pre-existing vs de novo?

• 771 kidney biopsy specimens from two North American and five European centers.

• 103 (50%) patients had preexisting DSA and 102 (50%) had de novo DSA.

• Compared with patients with preexisting DSA ABMR, patients with de novo DSA ABMR displayed increased proteinuria, more transplant glomerulopathy lesions, and lower glomerulitis, but similar levels of peritubular capillaritis and C4d deposition.

Auber O. et al., JASN, 2017
Pre-existing vs de novo?

Figure 3. Molecular biopsy scores according to DSA characteristics. Data are on the basis of 666 kidney allograft biopsies assessed for intragraft gene expression of the PBTs ([A] endothelial DSA-selective transcripts, [B] macrophage-inducible transcripts, [C] natural killer cell [NK] transcripts, [D] IFNγ production and inducing transcripts, [E] T cell transcripts, [F] injury-repair response transcripts) according to circulating anti-HLA DSA and ABMR status (reference set without ABMR, preexisting DSA ABMR, and de novo DSA ABMR). The T bars indicate SEM and DSA denotes anti-HLA DSA.

Auber O. et al., JASN, 2017
Does all dnDSA matter?

- DnDSA (6.3 years mean follow-up): 61% of them have shown signs of acute or indolent ABMR on indication or surveillance biopsy (Wiebe C. AJT, 2012)

- The presence of complement-binding IgG₁ and IgG₃ dnDSA generally negatively impacts long-term outcome and may be associated with 30% lower 5-year graft survival (Freitas MC, Transplantation, 2013)

- Presence of C₁q binding post-transplant DSA was associated with increased the risk of graft loss (HR: 4.78, 95%CI: 2.69-8.49) after adjustment for several immunological, histological and clinical factors (Loupy A., NEJM, 2013)
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Primary prevention

• Perform transplantation without pre-existing DSA
• Avoid transplantation with HLA mismatches, especially Class II HLA mismatches
• Avoid Class II EPLET mismatch
• Avoid non adherence (phone apps, selection)
• Avoid inappropriate reduction of ISU (immune monitoring)
• Early detection (new biomarkers?)
What is Eplet?

• Eplets are small configurations of polymorphic amino acid residues on human leukocyte antigen (HLA) molecules and are considered as essential components of HLA epitopes recognized by antibodies.

• **HLAMatchmaker** is a structurally based computer algorithm to determine HLA matching at the epitope level. ([http://www.epitopes.net/](http://www.epitopes.net/))
Relative Immunogenicity of HLA-C Epitopes

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<th>Eplet</th>
<th>Equivalent</th>
<th>Numbers of Mismatches</th>
<th>Reactive Eplets</th>
<th>Reactive as Pairs</th>
<th>Total</th>
<th>Antibody Frequency</th>
<th>Eplet</th>
<th>Equivalent</th>
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<td>93</td>
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Figure 3: Kaplan–Meier de novo DSA free survival curves. Panel (A) shows DR dnDSA free survival split by HLA-DRβ1/3/4/5 epitope mismatch quartiles. Panel (B) shows DQ dnDSA free survival split by HLA-DQα1/β1 epitope mismatch quartiles. Panel (C) shows DR dnDSA free survival split by an optimal mismatch cutoff of 10 mismatches for HLA-DRβ1/3/4/5 and in Panel (D) an optimal mismatch cutoff of 17 for HLA-DQα1/β1. dnDSA, de novo donor-specific antibody; HLA, human leukocyte antigen.
Adjusted for recipient age, recipient sex, peak PRA, recipient race, donor type, and induction

Sapir-Pichhadze R et al., AJT, 2014
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## Treatment options

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<th>Chronic ABMR treatment</th>
<th>Potential adverse events</th>
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<tr>
<td>1</td>
<td>PLEX</td>
<td>+</td>
<td>±</td>
<td>Hypotension, bleeding, hypovolemia</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>IVIG</td>
<td>+</td>
<td>±</td>
<td>Allergy, headache, myalgia, fever</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Rituximab (Rx)</td>
<td>++</td>
<td>+?</td>
<td>Infections, neutropenia, infusion reactions</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>Bortezomib (Bx)</td>
<td>ND</td>
<td>+++</td>
<td>Myelosuppression, neuropathy GI toxicity</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Eculizumab (Ex)</td>
<td>NA</td>
<td>+?</td>
<td>Meningococcal infection, hypertension</td>
<td>+++</td>
</tr>
<tr>
<td>6</td>
<td>Splenectomy (Sx)</td>
<td>++</td>
<td>+?</td>
<td>Infections, thrombocytosis</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>PLEX + IVIG</td>
<td>++</td>
<td>±</td>
<td>Additive</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>IVIG + Rx</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PLEX + IVIG + Rx</td>
<td>+++</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>PLEX + IVIG + Sx</td>
<td>+++</td>
<td>+?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>PLEX + IVIG + Rx + Bx</td>
<td>ND</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>PLEX + IVIG + Rx + Ex</td>
<td>NA</td>
<td>++++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND, no data; NA, not applicable; ±, occasional; ?, few data, not exactly known.

Remport A et al., NDT, 2015
Recent treatment practice

**TABLE 3 Immunosuppressive treatment combinations in transplant glomerulopathy**

<table>
<thead>
<tr>
<th>Treatment combinations</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + IVIG</td>
<td>4</td>
</tr>
<tr>
<td>Increase of immunosuppression (IS)</td>
<td>3</td>
</tr>
<tr>
<td>Plasmapheresis + Rituximab + IVIG</td>
<td>2</td>
</tr>
<tr>
<td>Rituximab + IVIG + Tacrolimus</td>
<td>2</td>
</tr>
<tr>
<td>Rituximab + Methylprednisolone</td>
<td>2</td>
</tr>
<tr>
<td>Methylprednisolone + Increase of IS</td>
<td>2</td>
</tr>
<tr>
<td>Everolimus</td>
<td>2</td>
</tr>
<tr>
<td>Plasmapheresis + Rituximab + IVIG + Tacrolimus + Increase of IS</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab + IVIG + Methylprednisolone + Everolimus</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab + IVIG + Methylprednisolone + Increase of IS</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab + IVIG + Methylprednisolone + Tacrolimus</td>
<td>1</td>
</tr>
<tr>
<td>Methylprednisolone + Tacrolimus + Increase of IS</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab + Tacrolimus + Increase of IS</td>
<td>1</td>
</tr>
<tr>
<td>IVIG + Methylprednisolone</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1</td>
</tr>
</tbody>
</table>

**FIGURE 1 Immunosuppressive drugs**

- 75% and 36.8% of kidney allograft failed at the end of follow-up.
- Treatment of transplant glomerulopathy proved ineffective to improve long-term kidney allograft survival (log rank=0.975; Figure 2).
- The administration of rituximab and IVIG alone or in combination did not improve either of the major outcomes (log rank=0.628; Figure 3).

- Single center, retrospective study with **48 patients** from Portugal.
- **Two-third of the patients have been treated.**
- The overall cumulative kidney **allograft survival at 10 years was 75%**.

Abreu R. et al., Clin Transpl, 2017
Rituximab

• Two recent clinical trials failed to show any benefit of Rituximab (Moreso F et al., AJT, 2017 and RITUX ERAH: Sautenet B. et al., Transplantation, 2016)

• RITUX ERAH: PLEX+IVIG+/- Rituximab (n=38)

• Moreso F: IVIG +/- Rituximab (n=25)

• No difference in death, graft loss, serum creatinine, proteinuria in 1,3,6,12 months
**FIGURE 3.**ITT analysis of serum creatinine level (µmol/L) over 1 year in the rituximab and placebo groups. Box height indicates the IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line is the median. The lower whisker represents the 25th percentile minus 1.5 times the IQR and the upper whisker the 75th percentile plus 1.5 times the IQR. Values outside the whiskers are outliers. IQR indicates interquartile range.

**FIGURE 4.**ITT analysis of proteinuria (mg/day) over 1 year in the rituximab and placebo groups. Box height indicates the IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line is the median. The lower whisker represents the 25th percentile minus 1.5 times the IQR and the upper whisker the 75th percentile plus 1.5 times the IQR. Values outside the whiskers are outliers.
### Table 1: Baseline demographic characteristics and alloantibody data in all patients

<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 ≤ 3months (n, %)</td>
<td>2 (7.7%)</td>
<td>21 (41%)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Patients developing high DSA levels ≤ 3 months</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 post-transplant</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) (maximum serum creatinine – nadir serum creatinine)</td>
<td>0.45 ± 0.37</td>
<td>0.93 ± 1.15</td>
<td>0.05</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>

**Notes:**
- ^1^ B flow crossmatch channel shift >350 at any time point in the first 3 months.
- ^2^ Race or ethnic group was self-reported; patients receiving pretransplant plasmapheresis were those with a baseline B- or T-cell flow cytometric crossmatch channel shift >300.
Plasma-Derived C1 Esterase Inhibitor

• Phase 2b, multicenter double-blind randomized placebo-controlled pilot study
• IVIG+PLEX +/- C1 Esterase Inhibitor for 2 weeks
• 9 patients in each arm
• 7/9 in C1 group and 6/9 in standard care group has resolved aABMR at day 20 biopsy
• 6 months biopsy in 14 patients: 0/7 has TG in C1 group and 3/7 in standard care group

Montgomery R. A. et al., AJT, 2016
Tocilizumab - Anti–Interleukin-6 Receptor Monoclonal Antibody?

- 36 renal transplant patients with cABMR plus DSAs and TG who failed standard of care treatment with IVIG plus rituximab with or without plasma exchange.
- Patients were offered rescue therapy with the anti–IL-6 receptor monoclonal tocilizumab with monthly infusions and monitored for DSAs and long-term outcomes.
- Tocilizumab-treated patients demonstrated graft survival and patient survival rates of 80% and 91% at 6 years, respectively.
- Significant reductions in DSAs and stabilization of renal function were seen at 2 years.
- No significant adverse events or severe adverse events were seen.

Choi J. et al., AJT, 2017
Tocilizumab - Anti–Interleukin-6 Receptor Monoclonal Antibody?

Choi J. et al., AJT, 2017

Figure 1. Kaplan-Meier curves of kidney allograft patient survival after initial treatment with tocolizumab for chronic active antibody-mediated rejection (cAMR). (A) Kidney all graft survival by treatment for all tocolizumab-treated cAM patients. (B) Graft survival for all tocolizumab-treated patient with transplant glomerulopathy (TG). (C) Patient survival for cAM patients treated with tocolizumab. Overall, tocolizumab was associated with good graft and patient survival.

Figure 2: Kaplan-Meier curves of kidney allograft an patient survival after initial treatment with tocolizumab for chronic active antibody-mediated rejection (cAMR). (A) Kidney all graft survival by treatment for all tocolizumab-treated cAM patients. (B) Graft survival for all tocolizumab-treated patient with transplant glomerulopathy. (C) Patient survival for cAM patients treated with tocolizumab. Overall, tocolizumab was associated with good graft and patient survival.

Choi J. et al., AJT, 2017
Transplant Glomerulopathy

• Common (5-20% low IR, up to 60% for high IR)
• Well described pathology (Banff 2013)
• Repeated endothelial injury and recovering
• Non adherence, inappropriate withdrawal of ISU, HLA and non-HLA antibodies
• Primary prevention (low IR Tx, good HLA match, medication adherence, EPLET matching)
• No effective and safe treatment
Questions?
TG impacts on outcome

**TABLE 1.**

<table>
<thead>
<tr>
<th>n</th>
<th>Age (years)</th>
<th>Male:fema</th>
<th>Body mass</th>
<th>Months o1</th>
<th>Second tra</th>
<th>Cadaveric:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HLA-A,B</td>
<td>HLA-DR</td>
<td>Panel reac</td>
<td>HBV-Ag</td>
<td>HCV-Ab</td>
<td>Original r</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Polycysti</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Urologi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Miscella</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Undetei</td>
</tr>
</tbody>
</table>

Data are n (a Controls b Chronic g

**FIGURE 2.** Pure graft survival excluding death in patients with TGP vs controls.

Banfi G et al., Transplantation, 2005
Table 1: Comparison of HLA-sensitized kidney transplant recipients and nonsensitized match control subjects

<table>
<thead>
<tr>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.69(^1)</td>
</tr>
<tr>
<td>1.0(^1)</td>
</tr>
<tr>
<td>0.82(^1)</td>
</tr>
<tr>
<td>0.002(^1)</td>
</tr>
<tr>
<td>0.005(^1)</td>
</tr>
<tr>
<td>(&lt;\ 0.001(^1)</td>
</tr>
<tr>
<td>(&lt;\ 0.001(^1)</td>
</tr>
<tr>
<td>1.0(^1)</td>
</tr>
<tr>
<td>0.37(^1)</td>
</tr>
</tbody>
</table>

Figure 1: Five-year outcomes after positive crossmatch live donor kidney transplant (+XMKTx). Actual 5-year outcomes are shown for +XMKTx including patient survival (panel A); overall death-censored graft survival (panel B); grafts survival by baseline crossmatch assay type (+XMKTx recipients who were CDC + vs. CDC −, panel C); and graft survival by donor-specific HLA specificity (+XMKTx recipients with antibody against donor class I only, class II only and both class I and II, panel D). (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.
Banff 2013 classification, the biopsy diagnosis of cABMR should meet three criteria

• presence of donor-specific alloantibodies,
• demonstration of alloantibody interaction with vascular endothelium: complement 4d-positivity in peritubular capillaries and/or at least moderate microvascular inflammation (MVI) and/or increased gene expression of endothelial activation and injury transcripts (ENDATs),
• morphologic signs of alloantibody-induced chronic vascular injury: transplant glomerulopathy and/or severe peritubular capillary basement membrane multilayering and/or new onset arterial intimal fibrosis.

Haas M et al., AJT, 2014
Early and Overt Transplant Glomerulopathy

Box 1. Diagnostic Criteria for Early Transplant Glomerulopathy

**Light microscopy (nondiagnostic)**
- No double contours or double contours in <10% of peripheral capillary loops in the most severely affected glomerulus
- None to mild mesangial matrix expansion
- Glomerulitis and/or peritubular capillaritis usually are present

**Immunofluorescence (nondiagnostic)**
- Negative for significant IgA, IgG, and C1q
- Sometimes mild to moderate mesangial IgM staining and minimal mesangial or capillary loop C3 staining
- C4d ± in peritubular capillaries by immunofluorescence or immunohistochemistry
- C4d ± in glomerular capillaries by immunofluorescence or immunohistochemistry

**Electron microscopy (diagnostic after correlation with the methods above)**
- Few peripheral glomerular loops with duplication and/or multilayering of glomerular basement membranes present, in the absence of immune complexes, with any of the following features:
  ◊ Widening of subendothelial space
  ◊ Endothelial cell swelling
  ◊ Loss of endothelial cell fenestrations
  ◊ None to mild mesangial matrix expansion

*Note:* Early transplant glomerulopathy corresponds to a Banff cg score of 0.

Box 2. Diagnostic Criteria for Overt Transplant Glomerulopathy

**Light microscopy**
- Double contours in >10% of peripheral capillary loops in the most affected nonsclerotic glomeruli
- Mesangial matrix expansion is usually present, with/without mesangial hypercellularity
- Glomerulitis and/or peritubular capillaritis may be present

**Immunofluorescence**
- Negative for significant IgA, IgG, and C1q
- Sometimes mild to moderate mesangial IgM staining and minimal mesangial or capillary loop C3 staining
- C4d ± in peritubular capillaries by immunofluorescence or immunohistochemistry
- C4d ± in glomerular capillaries by immunofluorescence or immunohistochemistry

**Electron microscopy**
- Several peripheral glomerular loops with duplication and/or multilayering of glomerular basement membranes present, in the absence of immune complexes, usually with any of the following features:
  ◊ Widening of subendothelial space
  ◊ Mesangial cell interposition
  ◊ Endothelial cell swelling
  ◊ Loss of endothelial cell fenestrations

*Note:* Overt transplant glomerulopathy corresponds to a Banff cg score higher than 0. Light microscopy should be correlated with immunofluorescence and/or electron microscopy for diagnosis.

Husain S and Sis B, AJKD, 2013
Personalized approach based on EPLET?

- **654 adult and pediatric** consecutive renal transplant recipients from Canada.
- Eplets identified by **HLAMatchmaker** software.
- Post-transplant serum samples were collected and stored at **0, 1, 2, 3, 6, 12, 18, and 24 months** and then yearly or at the time of biopsy for graft dysfunction.

### Table 2. Multivariate correlates of dnDSA development: Total cohort

<table>
<thead>
<tr>
<th>Total Cohort</th>
<th>DR dnDSA ( n=596, 29 ) Events</th>
<th>DQ dnDSA ( n=596, 51 ) Events</th>
<th>DR or DQ dnDSA ( n=596, 66 ) Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Recipient age at transplant, yr</td>
<td>0.97 (0.95 to 0.99)</td>
<td>0.02</td>
<td>0.97 (0.95 to 0.98)</td>
</tr>
<tr>
<td>Nonadherence</td>
<td>3.07 (1.40 to 6.52)</td>
<td>&lt;0.01</td>
<td>3.11 (1.71 to 5.58)</td>
</tr>
<tr>
<td>Cyclosporin versus tacrolimus</td>
<td>2.14 (0.93 to 4.70)</td>
<td>0.07</td>
<td>1.97 (1.06 to 3.52)</td>
</tr>
<tr>
<td>HLA-DRB(_1)/3/4/5 eplet mismatch/ten mismatches</td>
<td>2.79 (1.84 to 4.27)</td>
<td>&lt;0.001</td>
<td>2.00 (1.52 to 2.67)</td>
</tr>
<tr>
<td>HLA-DQ(_\alpha_1)/(\beta_1) eplet mismatch/ten mismatches</td>
<td></td>
<td></td>
<td>1.37 (1.18 to 1.58)</td>
</tr>
<tr>
<td>HLA-DRB(<em>1)/3/4/5 + HLA-DQ(</em>\alpha_1)/(\beta_1) eplet mismatch/ten mismatches</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wiebe C. et al., JASN, 2017
Personalized approach based on EPLET?

Figure 6. Eplet mismatch modulates the effect of tacrolimus trough levels on the development of dnDSA. High risk: HLA-DR or -DQ eplet mismatch >11; low risk: HLA-DR and -DQ eplet mismatch ≤11. P values represent a comparison of high-risk patients who developed dnDSA with high-risk patients who did not develop dnDSA and a comparison of high-risk patients who developed dnDSA with low-risk patients who did not develop dnDSA. Values represent the mean percentages of tacrolimus trough levels below each threshold and their corresponding 95% confidence intervals.
Rituximab

Ishida H. et al., Transpl Int, 2014

(a) Cumulative probability

(b) Cumulative probability

Log-rank test: 0.034

DSA positive/rituximab

2001~2005

N = 39, 110

Group 1 (DSA + Rit -), Group 2 (DSA - Rit -), Group 3 (DSA + Rit +), Group 4 (DSA - Rit +)

N = 3
IgG endopeptididase?

Jordan S. C. et al., NEJM, 2017
Potential future drugs

- anti-CD20 antibody ocrelizumab
- anti-CD22 antibody epratuzumab
- humanized monoclonal anti-BlyS antibody belimumab
- APRIL and BlyS ligand inhibiting immunoglobulin fusion protein atacicept

Remport A et al., NDT, 2015