Update on Transplant Glomerulopathy

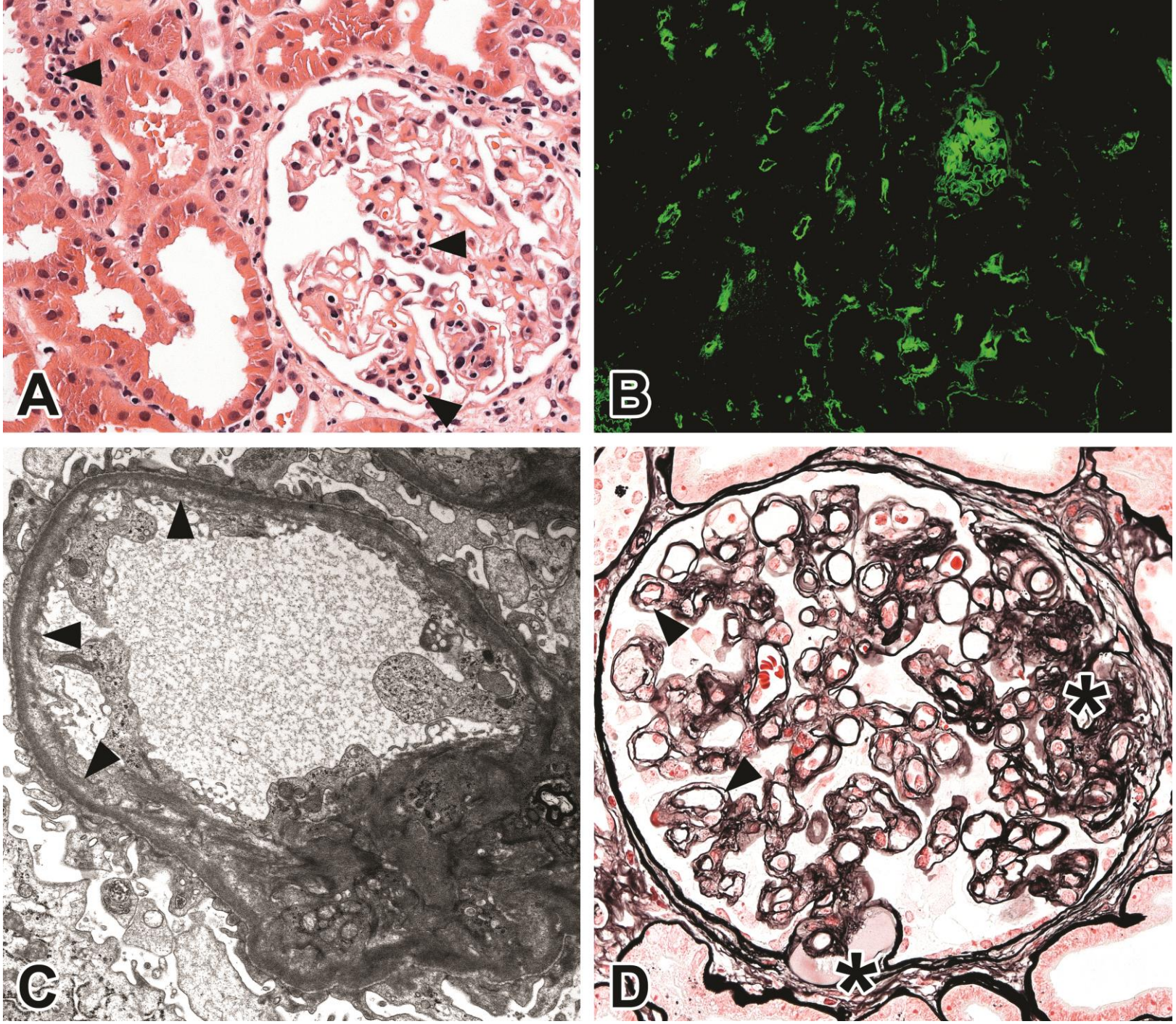
Miklos Z Molnar, MD, PhD, FEBTM, FERA, FASN
Associate Professor of Medicine
Methodist University Hospital, Transplant Institute
Division of Transplantation, Department of Surgery
University of Tennessee Health Science Center
Memphis, TN, USA

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:


A
B
C
D

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

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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.

Redfield R.R. et al., Hum. Immun., 2016

cABMR effects on outcome using Banff - 2013

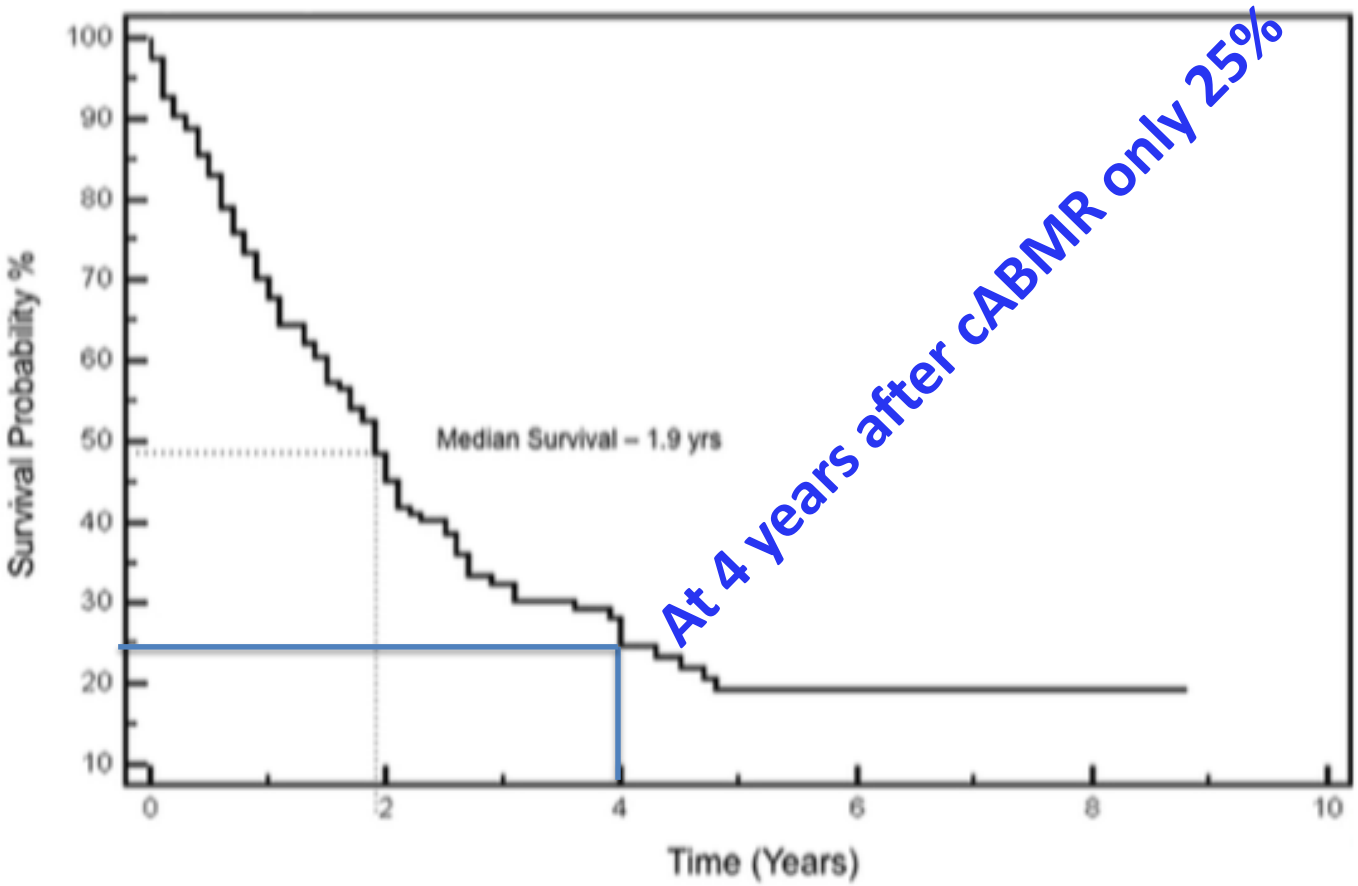


Fig. 3. Kidney graft survival following cAMR diagnosis.

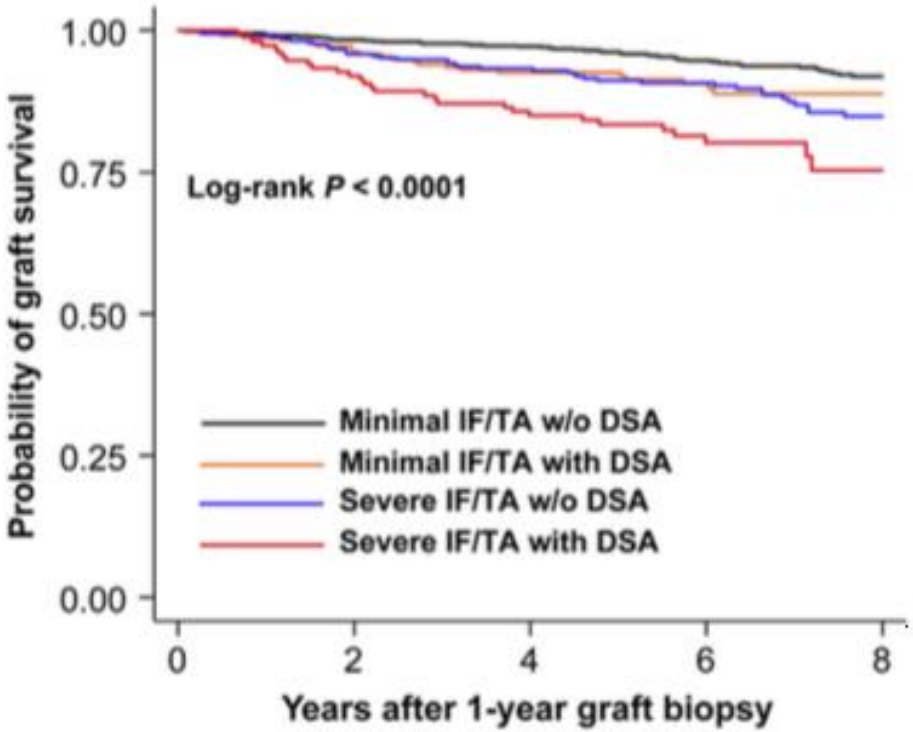
Redfield R.R. et al., Hum. Immun., 2016

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



Number at risk					
	817	766	718	515	271
	224	209	191	104	23
	344	314	280	188	95
	154	134	119	66	16

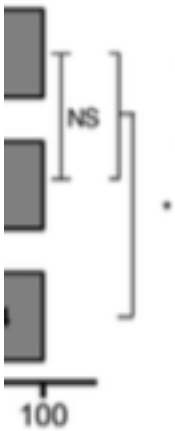


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Figure 6 | Kaplan-Meier estimates for death-censored kidney allograft survival according to 1-year posttransplantation interstitial fibrosis and tubular atrophy (IF/TA) severity and anti-human leukocyte antigen donor-specific antibody (DSA) status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

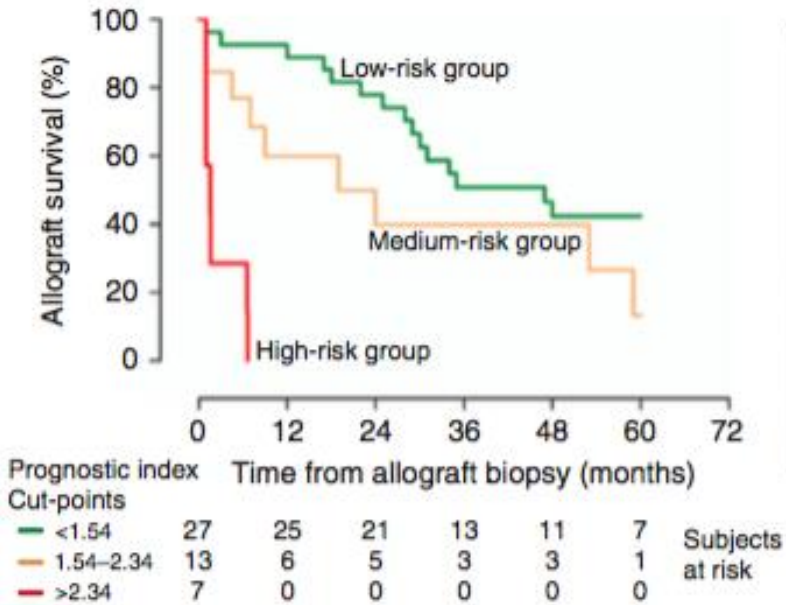
Gosset C. et al., KI, 2017

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?



Months	Allograft survival		
	Risk groups		
	Low	Medium	High
6	93%	77%	29%
12	89%	62%	0%
24	78%	41%	0%
36	52%	41%	0%
48	44%	41%	0%
60	44%	14%	0%

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.

various time points after the diagnosis. PI, prognostic index.

Patri P. et al., KI, 2016

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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:

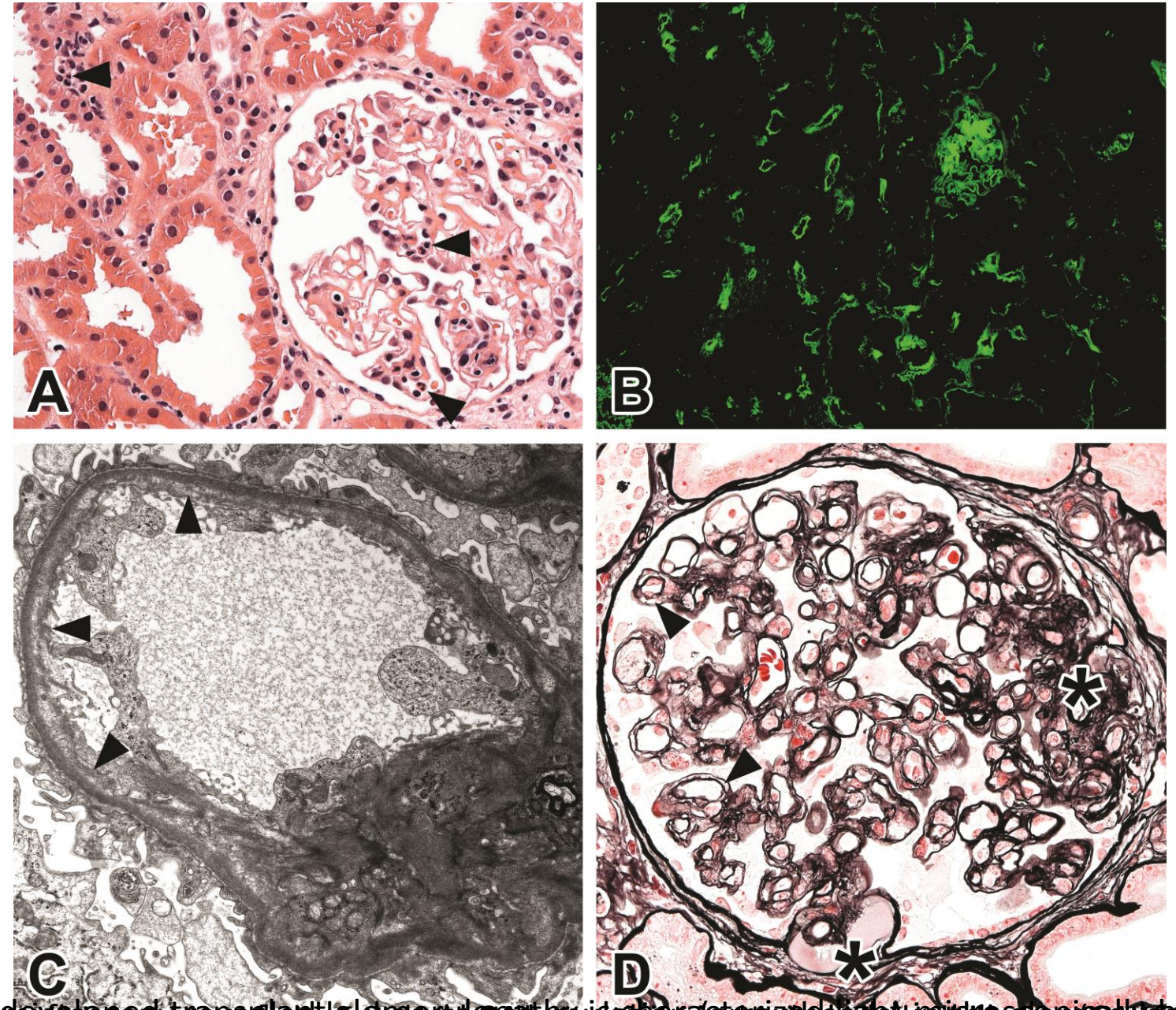
1. Transplant glomerulopathy (cg >0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis, includes changes evident by PAS staining on paraffin sections)
2. Arterial intimal fibrosis of new onset excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required

Evidence of **current/recent antibody interaction with vascular endothelium,** *including 1 or more of the following:*

- Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, C4d staining on paraffin sections)
- At least moderate intravascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
- **Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, *if thoroughly validated***

C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met

Haas M et al., AJT, 2018



(A) Light microscopy (periodic acid-Schiff stain) showing capillary loops (arrowheads). (B) Immunofluorescence (IgG stain) showing capillary loops (arrowheads). Asterisks indicate subcentral, red-stained capillary lumens, and the deposition of glomerular basement membrane along the entire capillary circumference (arrowhead) in three loops.

(C) Electron microscopy showing capillary loops (arrowheads) with diffuse, electron-dense deposits, and the presence of widespread double contours of capillary loops (arrowheads). Asterisks indicate subcentral, red-stained capillary lumens, and the deposition of glomerular basement membrane along the entire capillary circumference (arrowhead) in three loops.

(D) Well-developed transplant glomerulopathy (periodic acid-Schiff stain) showing capillary loops (arrowheads) with diffuse, electron-dense deposits, and the presence of widespread double contours of capillary loops (arrowheads). Asterisks indicate subcentral, red-stained capillary lumens, and the deposition of glomerular basement membrane along the entire capillary circumference (arrowhead) in three loops.

(E) Light microscopy showing glomerular capillaries with diffuse, electron-dense deposits (arrowheads) and loss of fenestrae (original magnification, x 400).

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!)

Remport A et al., NDT, 2015

HCV+ and C4d+ TG

Table 1 | Pathological features of patients with TG according to HCV and C4d status

n=16; %)	HCV⁺TG (n=9; %)	C4d⁻TG (n=13)	C4d⁺TG (n=12)
100%)	9 (100%)	13 (100%)	12 (100%)
69%)[a]	2 (22%)[a]	8 (62%)	5 (42%)
71%)	5/7 (71%)	10/13 (77%)	5/8 (63%)

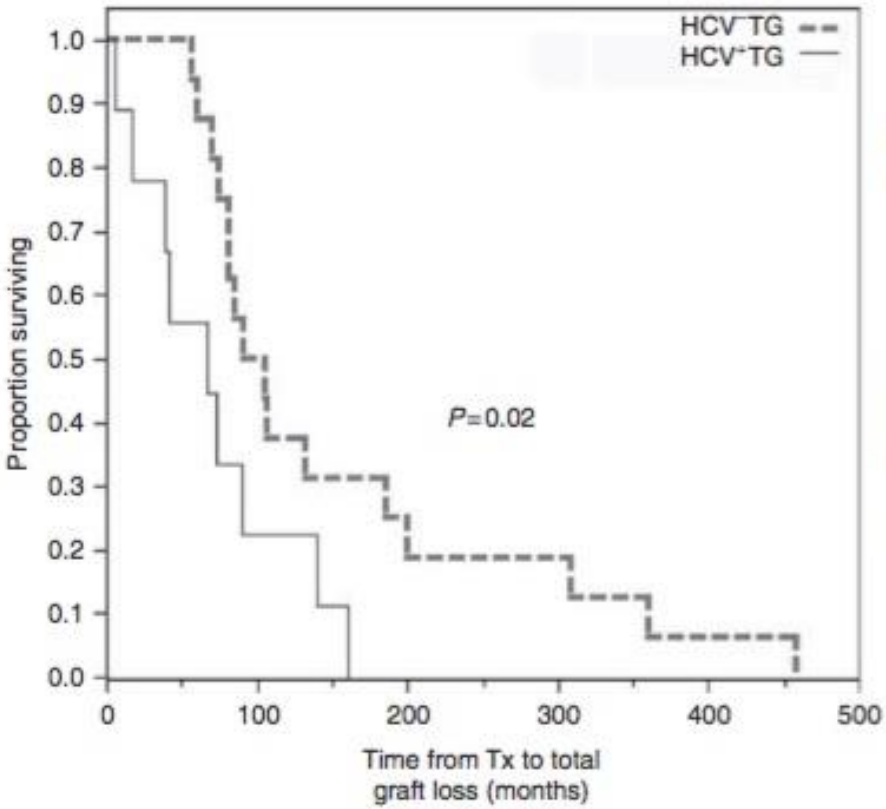


Figure 2 | Kaplan–Meier curves showing time to graft loss after transplantation in HCV⁻TG and HCV⁺TG patients. HCV⁺TG patients had a significantly faster progression to graft failure after Tx as compared with HCV⁻TG patients. HCV, hepatitis C virus; TG, transplant glomerulopathy; Tx, transplantation.

Table 3 | Multivariate analysis of clinicopathological factors and time to graft loss

	Likelihood ratio (P-value) based on proportional hazards (Cox) fit	Likelihood ratio (P-value) based on parametric survival fit
C4d	0.82 (P=0.36)	1.86 (P=0.17)
TMA	0.14 (P=0.71)	0.29 (P=0.59)
HCV	4.56 (P=0.03)	5.06 (P=0.02)

Abbreviations: HCV, hepatitis C virus; TMA, thrombotic microangiopathy.

(n=16)	HCV⁺TG (n=9)	P-value
117.0	61.0 ± 46.2	0.07
edian 3.4)	4.6 ± 1.9 (median 3.8)	0.74
1.1	2.3 ± 2.3	0.73
	4 (44%)	0.01
0%)	9 (100%)	1.00
%)	9 (100%)	1.00
34.9	10.1 ± 15.8	0.07
120.5	71.1 ± 52.7	0.03
6)	1 (11%)	1.00

, transplantation.

Baid-Agrawal et al., KI, 2011

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Common pathway in pathophysiology

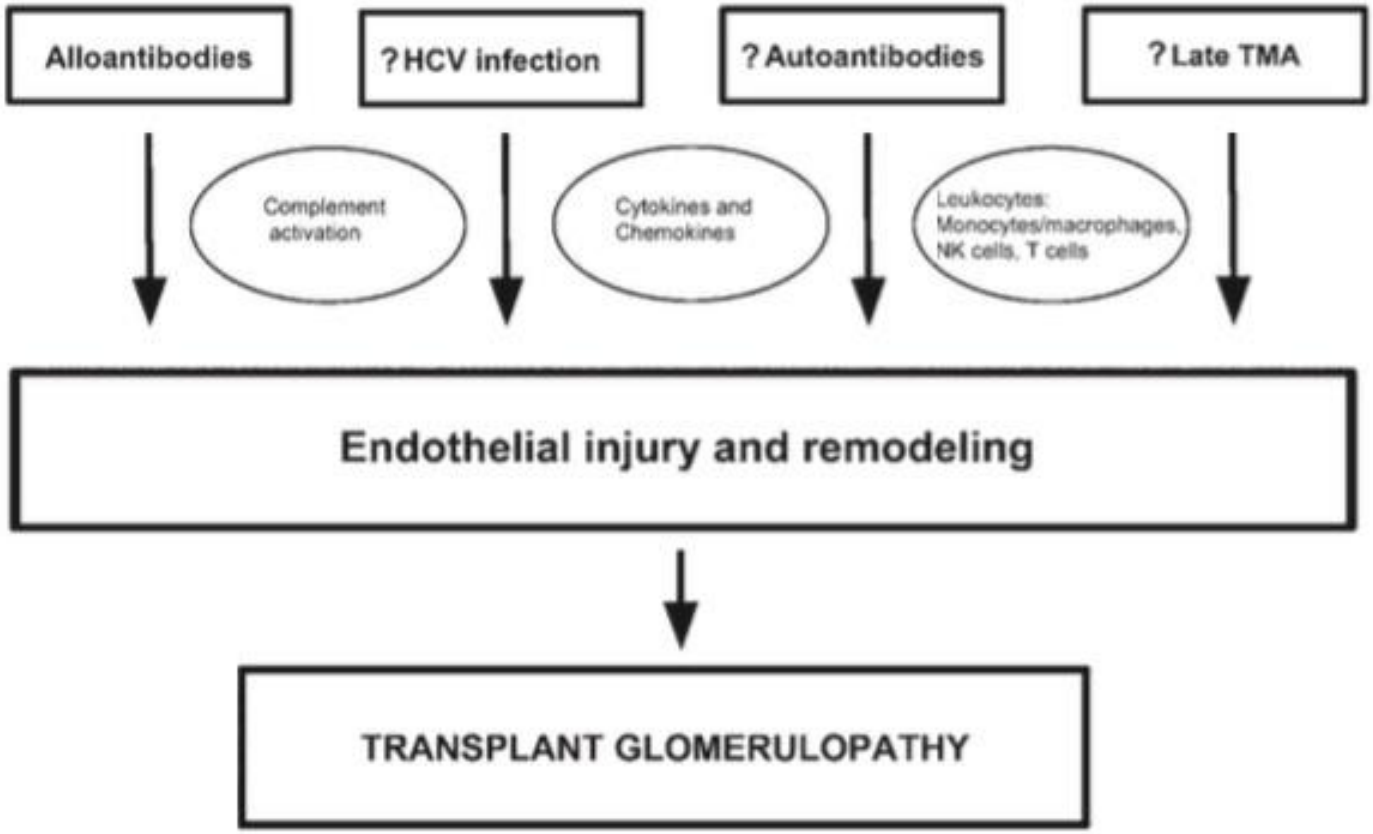


Figure 2. A schematic representation of the working proposal of evidence-based etiopathogenesis of transplant glomerulopathy. Abbreviations: HCV, hepatitis C virus infection; NK, natural killer cells; TMA, thrombotic microangiopathy.

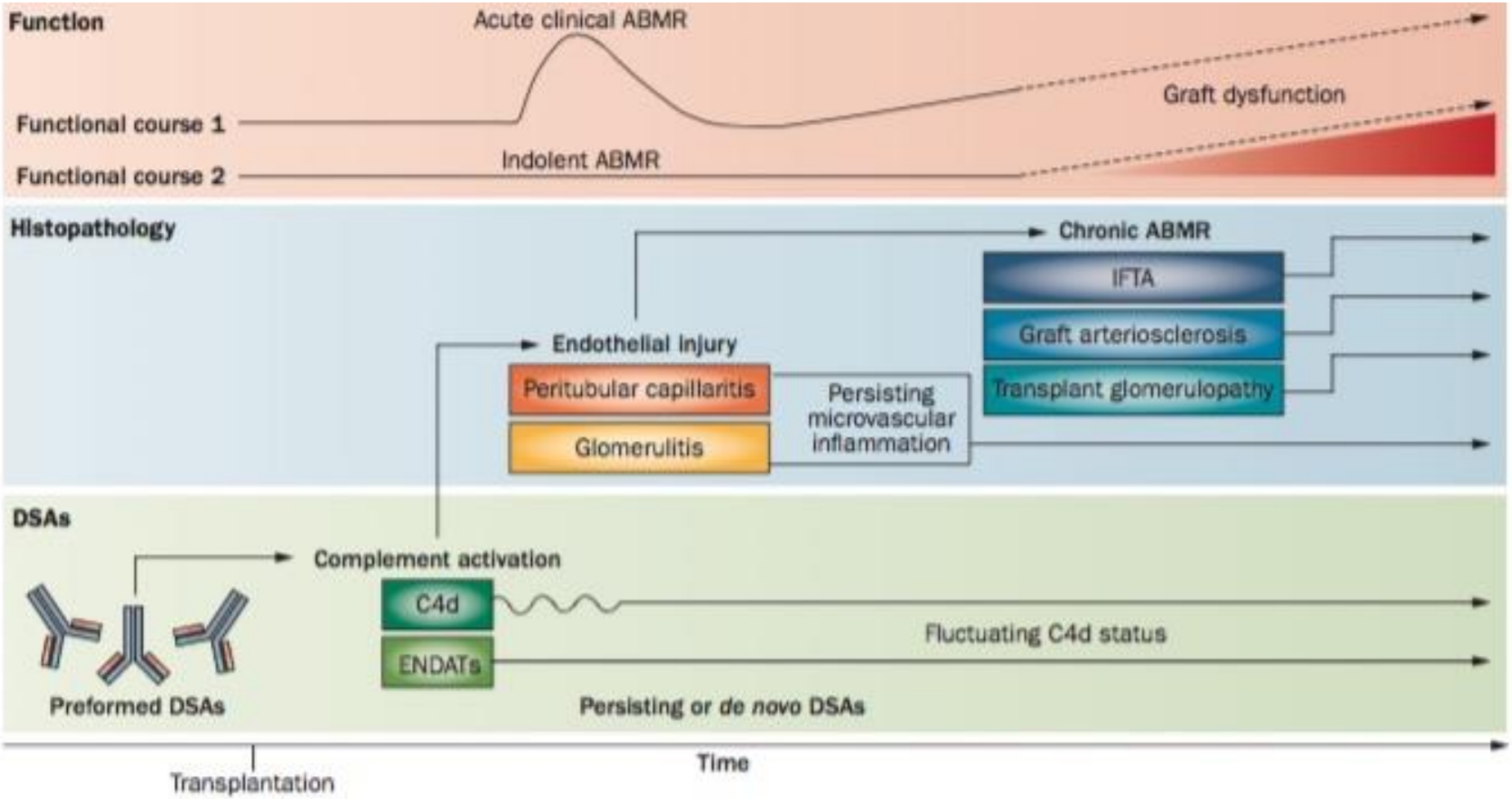
Husain S and Sis B, AJKD, 2013

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



Loupy A. et al., Nat. Rev. Nephrol., 2012

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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

De novo DSA

TABLE 2. Baseline patient characteristics

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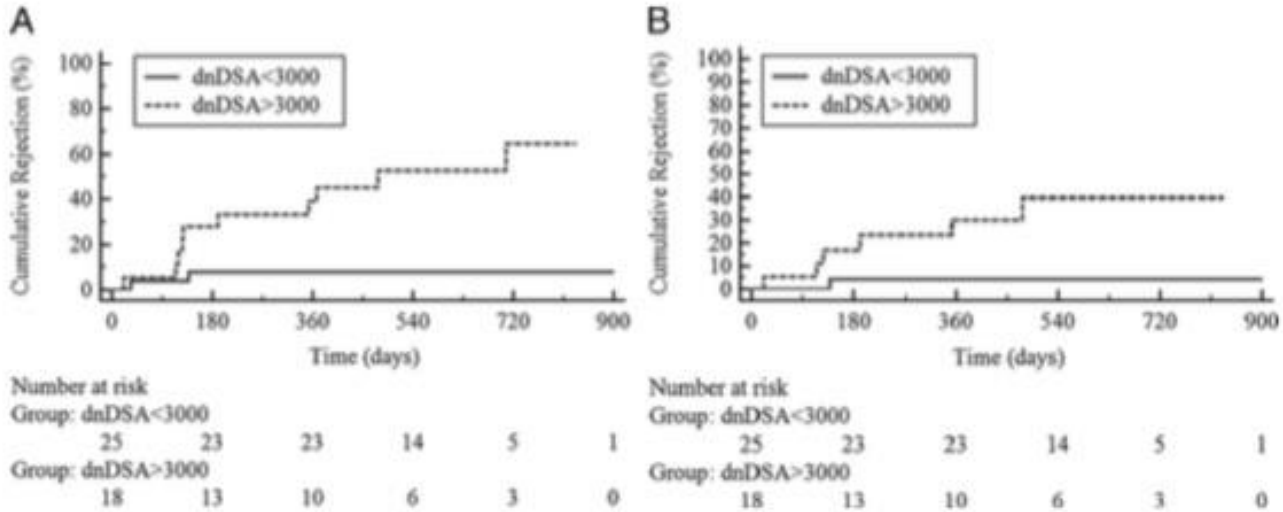

FIGURE 1. Impact of the MFI level of the dnDSA on the risk of rejection. A, The group with an MFI greater than or equal to 3,000 has a higher risk for all rejection (cellular or antibody mediated) (HR, 8.61; 95% confidence interval, 2.67–27.8; log-rank P=0.0008). B, the risk of AMR (includes AMR or mixed 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.

reactive antibody.

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?

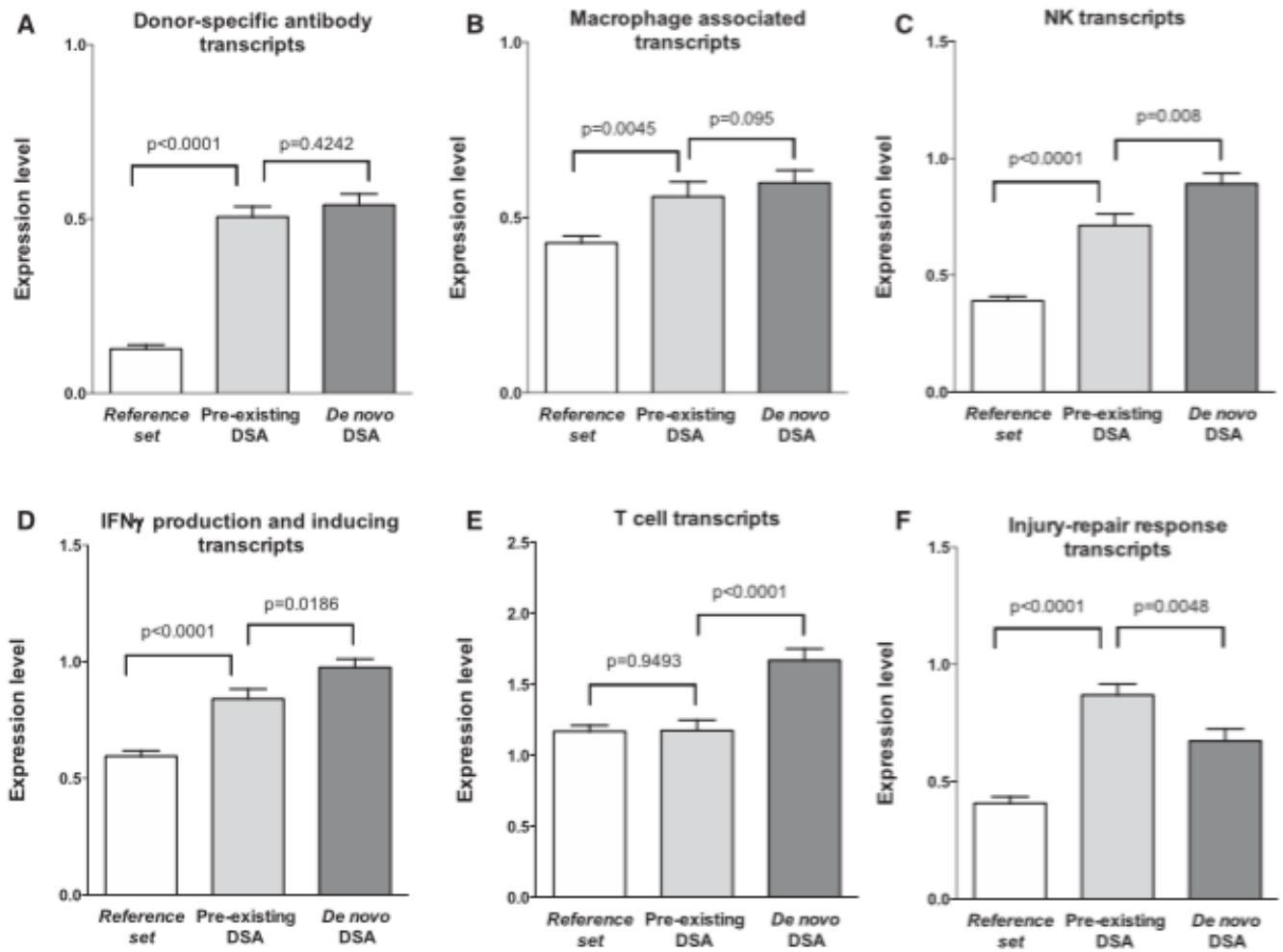

Figure 3. Molecular biopsy scores according to DSA characteristics. Data are on the basis of 666 kidney allograft biopsies assessed for intragraft gene expression of the PBTs ([A] endothelial DSA-selective transcripts, [B] macrophage-inducible transcripts, [C] natural killer cell [NK] transcripts, [D] 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 IgG_1 and IgG_3 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/)

Relative Immunogenicity of HLA-C Epitopes

Eplet	Equivalent	Numbers of Mismatches	Reactive Eplets	Reactive as Pairs	Total	Antibody Frequency	Eplet	Equivalent	Numbers of Mismatches	Reactive Eplets	Reactive as Pairs	Total	Antibody Frequency
79RK	TerEp#244	14	8	4	12	86%	35Q		10	2	0	2	20%
138K		10	8	0	8	80%	73AS		11	2	0	2	18%
76TVN		10	7	0	7	70%	69RA		7	0	1	1	14%
173K	TerEp#5081	11	7	0	7	64%	193PV		8	1	0	1	13%
177KT	TerEp#40	10	6	0	6	60%	77VSN		10	0	1	1	10%
14WR		6	3	0	3	50%	79VRN	TerEp#246	10	0	1	1	10%
73AN	TerEp#5037	9	4	0	4	44%	184H		11	1	0	1	9%
193PL	TerEp#37	12	5	0	5	42%	116F		12	1	0	1	8%
21H	TerEp#39	14	5	0	5	36%	267QE		12	1	0	1	8%
151ARE		6	1	1	2	33%	69RT		14	1	0	1	7%
69KRQ		7	1	1	2	29%	151ARA		14	1	0	1	7%
77TVS	TerEp#421	14	3	1	4	29%	9D		11	0	0	0	0%
156RA		11	0	3	3	27%	9Y		4	0	0	0	0%
147L		8	2	0	2	25%	12AVR		10	0	0	0	0%
156WA		8	0	2	2	25%	71AT		10	0	0	0	0%
163EW	TerEp#222	4	1	0	1	25%	90D		9	0	0	0	0%
163LW	TerEp#245	4	1	0	1	25%	103L		5	0	0	0	0%
166LE		4	1	0	1	25%	113YD		7	0	0	0	0%
219W	TerEp#5075	13	3	0	3	23%	113YN		12	0	0	0	0%
35Q		10	2	0	2	20%	Total		372	78	15	93	25%

Duquesnoy and Marrari, *Transplant Immunology* 24: 164-71, 2011

Eplet matching

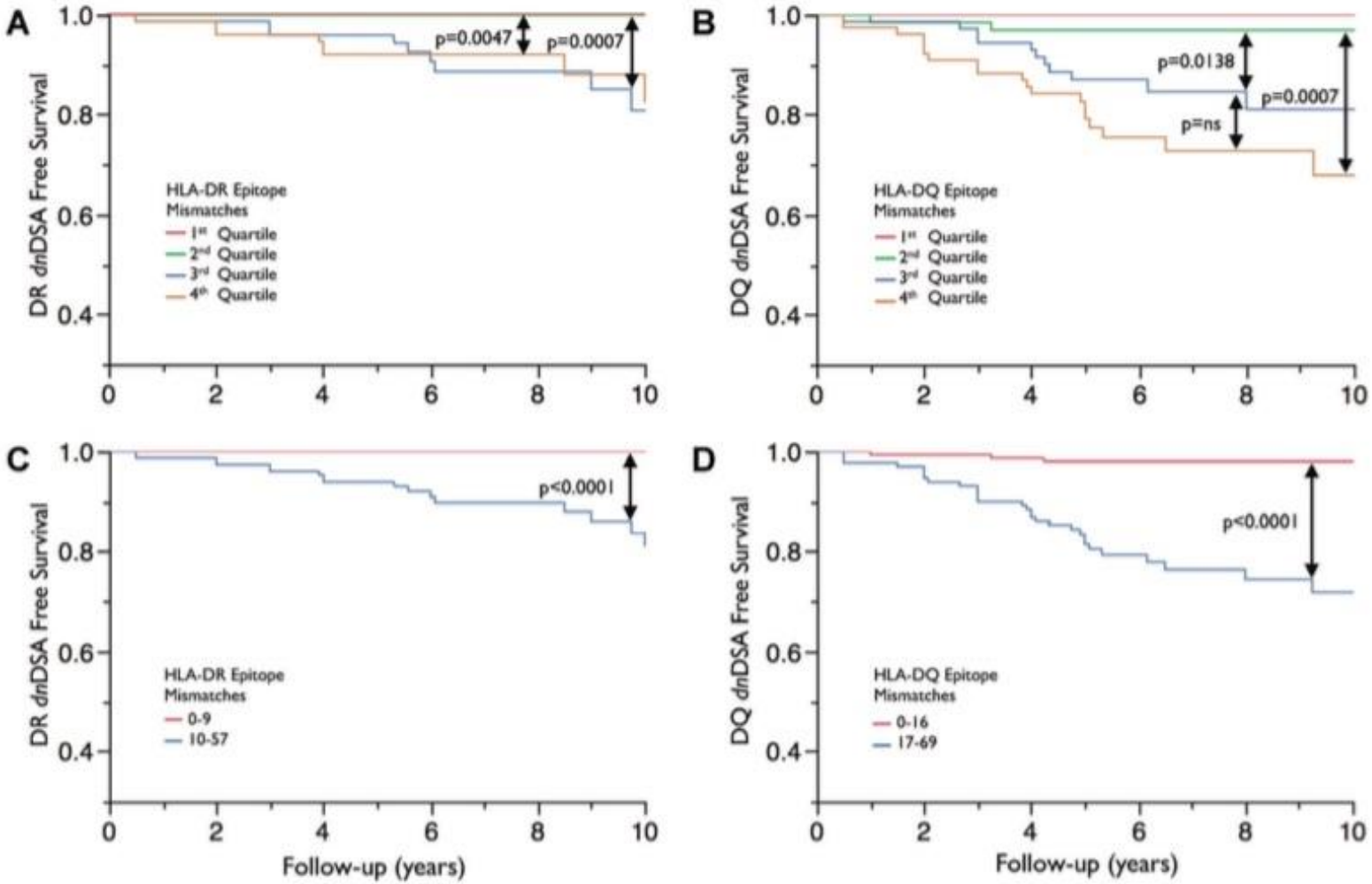

Figure 3: Kaplan–Meier *de novo* DSA free survival curves. Panel (A) shows DR *dn*DSA free survival split by HLA-DR$\beta_{1/3/4/5}$ epitope mismatch quartiles. Panel (B) shows DQ *dn*DSA free survival split by HLA-DQα_1/β_1 epitope mismatch quartiles. Panel (C) shows DR *dn*DSA free survival split by an optimal mismatch cutoff of 10 mismatches for HLA-DR$\beta_{1/3/4/5}$ and in Panel (D) an optimal mismatch cutoff of 17 for HLA-DQα_1/β_1. *dn*DSA, *de novo* donor-specific antibody; HLA, human leukocyte antigen.

Table 2: M

Model	p-Value
A: Clinical	<0.001
	<0.001
	<0.001
	<0.001
	<0.001
	<0.01
B: Epitope (adherer n = 247)	<0.02
	NS
	<0.01
	NS
	<0.02
	<0.02

[1]Odds rati

Figure 1

Wiebe C. et al., AJT, 2013

Eplet matching

Main Exposure	Unadjusted		Adjusted	
	OR [95%CI]	P-value	OR [95%CI]	P-value
HLA-DR+DQ eplet mismatch category				
<27	referent		referent	
27-43	2.59 [1.09, 6.17]	0.032	2.84 [1.03, 7.84]	0.043
>43	2.14 [0.88, 5.24]	0.095	4.62 [1.51, 14.14]	0.007
HLA-DQ eplet mismatch category				
<11	referent		referent	
11-21	2.90 [1.20, 6.97]	0.018	3.72 [1.33, 10.43]	0.012
>21	1.19 [0.48, 3.00]	0.713	2.39 [0.79, 7.21]	0.124
HLA-DR eplet mismatch category				
<13	referent		referent	
13-27	3.33 [1.43, 7.75]	0.005	3.61 [1.33, 9.80]	0.012
>27	3.44 [1.43, 8.28]	0.006	5.61 [1.87, 16.93]	0.002

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

Table 1. Efficacy and side effects of interventions for the prevention or treatment of antibody-mediated graft injury

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

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

Treatment combinations	n
Rituximab + IVIG	4
Increase of immunosuppression (IS)	3
Plasmapheresis + Rituximab + IVIG	2
Rituximab + IVIG + Tacrolimus	2
Rituximab + Methylprednisolone	2
Methylprednisolone + Increase of IS	2
Everolimus	2
Plasmapheresis + Rituximab + IVIG + Tacrolimus + Increase of IS	1
Rituximab + IVIG + Methylprednisolone + Everolimus	1
Rituximab + IVIG + Methylprednisolone + Increase of IS	1
Rituximab + IVIG + Methylprednisolone + Tacrolimus	1
Methylprednisolone + Tacrolimus + Increase of IS	1
Rituximab + Tacrolimus + Increase of IS	1
IVIG + Methylprednisolone	1
Rituximab	1

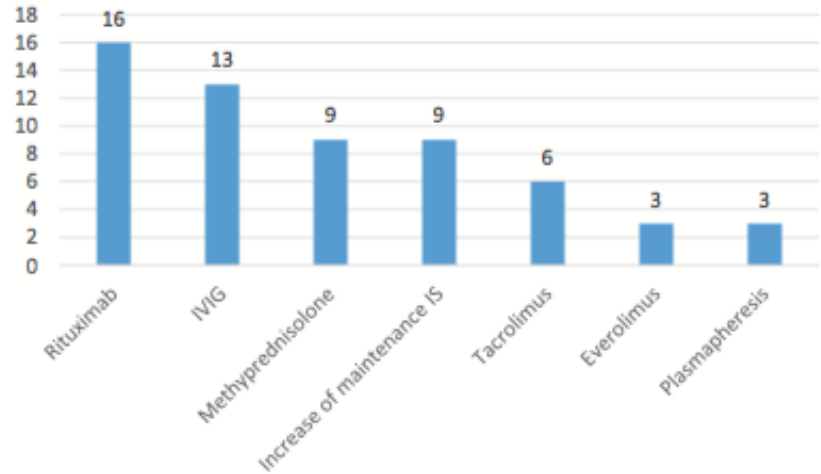

FIGURE 1 Immunosuppressive drugs

of 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

Rituximab

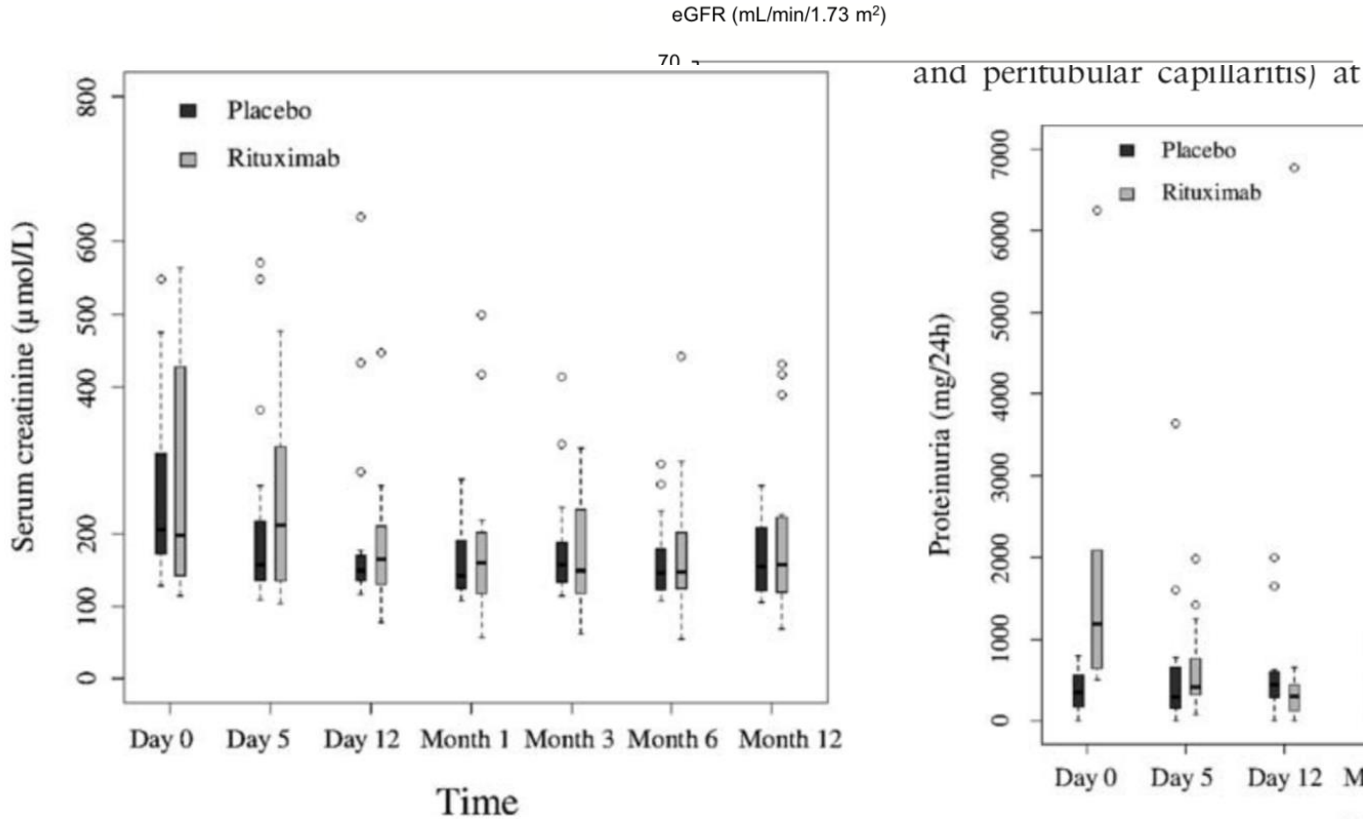

FIGURE 3. ITT analysis of serum creatinine level (µmol/L) over 1 year in the rituximab and placebo groups. Box height indicates the IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line is the median. The lower whisker represents the 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.

and peritubular capillaritis) at 6 months in the rituximab

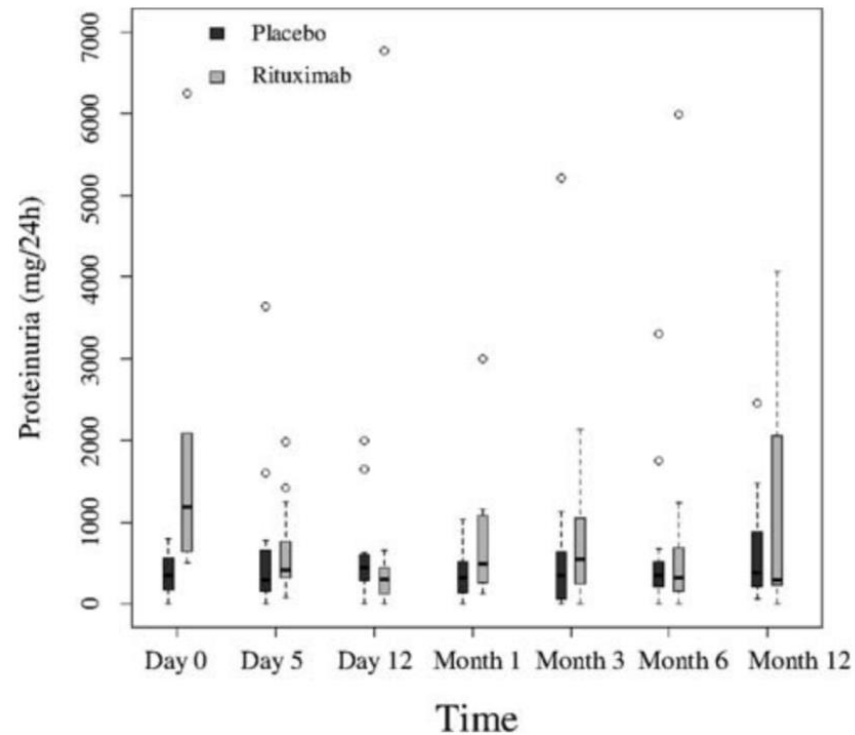

FIGURE 4. ITT analysis of proteinuria (mg/day) over 1 year in the rituximab and placebo groups. Box height indicates the IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line is the median. The lower whisker represents the 25th percentile 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.

Sautenet B et al, Trans Int, 2017
Boresi F et al, AJT, 2016

Eculizumab

Table 1: Baseline demographic characteristics and alloantibody data in all patients

Table 2: Posttransplant outcomes in the eculizumab-treated and control groups

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

[1]B flow crossmatch channel shift >350 at any time point in the first 3 months.

conti ment

was

Number of PEs (mean ± SD)	4.0 ± 3.6	3.7 ± 3.4	0.76

[1]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.

Stegall M.D. et al., AJT, 2011

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?

Graft Survival since dx of cABMR :~80%

Graft Survival since dx of TG:~70%

Patient Survival since dx of cABMR :~90%

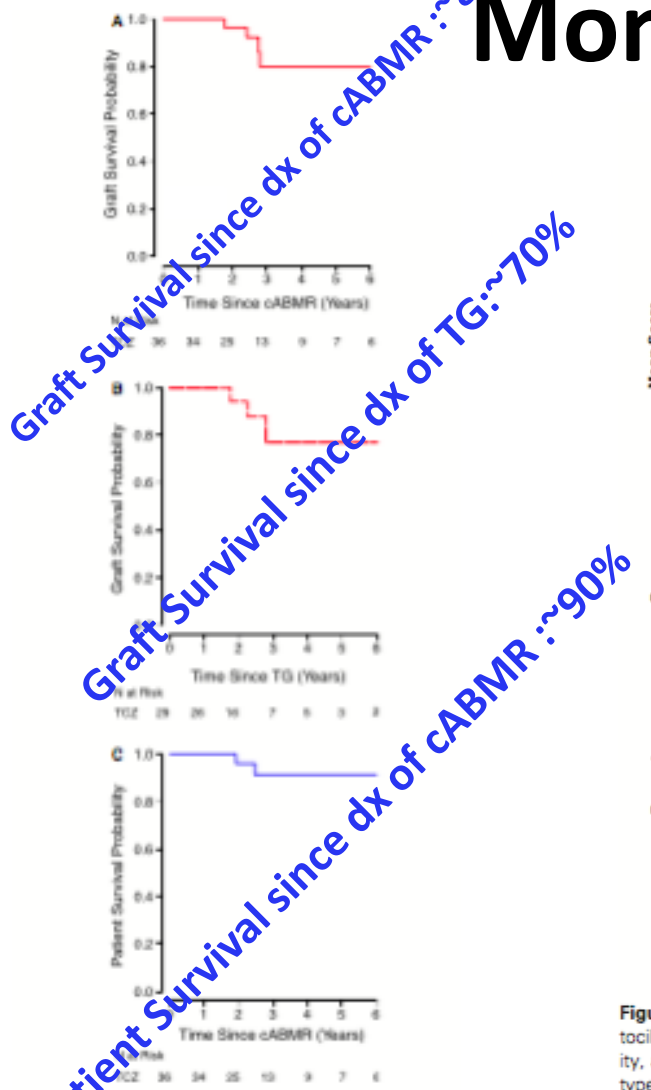

Figure 2: Kaplan–Meier curves of kidney allograft an patient survival after treatment with tocilizumab for chroni active antibody-mediated rejection (cAMR). (A) Kidney all graft survival by treatment for all tocilizumab-treated cAM patients. (B) Graft survival for all tocilizumab-treated patient with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

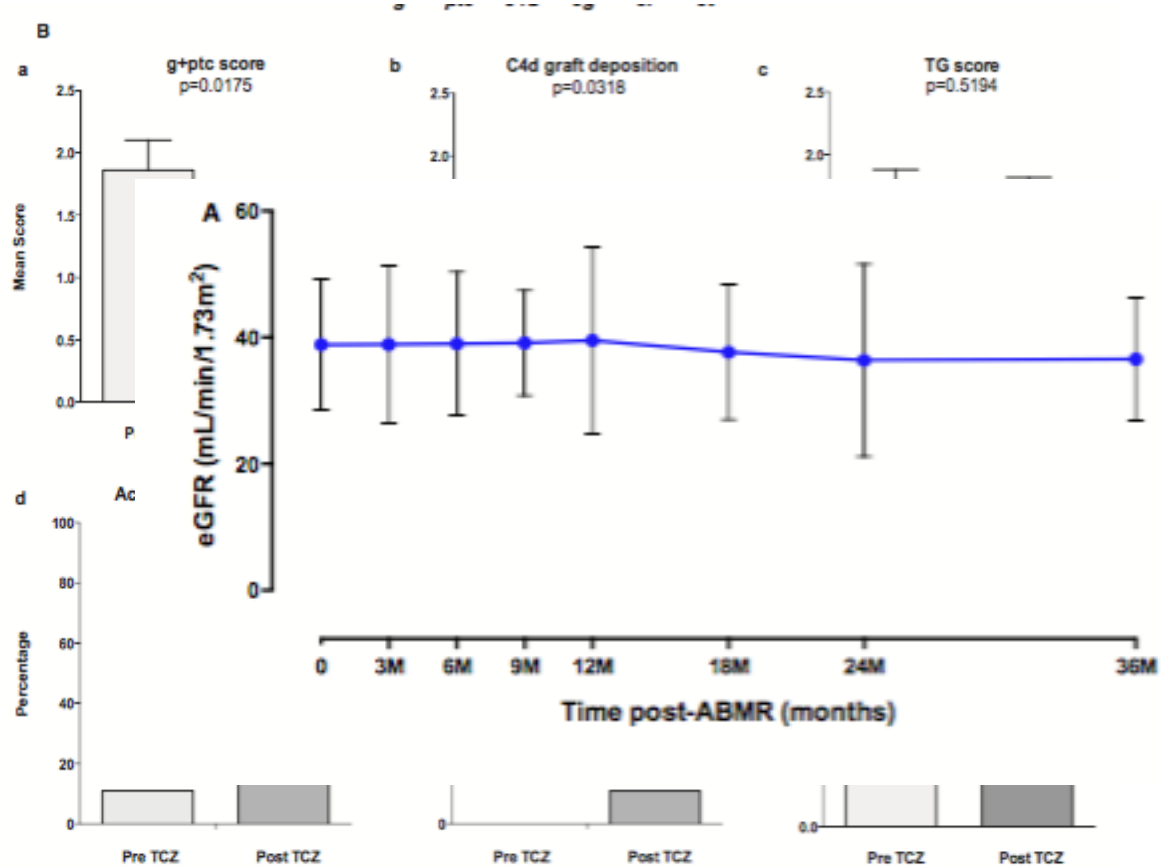

Figure 1: Index and 1 year post–tocilizumab allograft biopsies. (A) Kidney allograft index biopsy phenotypes at the initiation of tocilizumab treatment were obtained for 36 patients. All patients had significant glomerulitis (g), peritubular capilaritis (ptc), C4d positivity, and chronic changes in the glomerulus (cg), interstitium (ci), and tubules (ct). (B) This figure shows kidney allograft biopsy phenotypes before and after tocilizumab treatment (N = 9). Allograft biopsy specimens were obtained 1 year after tocilizumab treatment and compared with pretocilizumab chronic active antibody-mediated rejection biopsy specimens in nine patients. Significant reductions in g plus ptc scores and C4d deposition were seen with tocilizumab treatment. Other parameters were stable. TG, transplant glomerulopathy; IF/TA, Interstitial fibrosis/tubular atrophy.

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


Methodist
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Questions?

TG impacts on outcome

TABLE 1.

	P value
n	
Age (years	0.63
Male:fema	0.81
Body mass	0.33
Months or	0.28
Second tra	0.04
Cadaveric:	
HLA-A.B	0.49
HLA-DR	0.18
Panel reac	0.18
HBV-Ag p	0.31
HCV-Ab p	0.10
Original r	
Chronic	0.30[b]
Polycyst	
Urologi	
Miscella	
Undeter	

Data are n (
[a] Controls v
[b] Chronic g

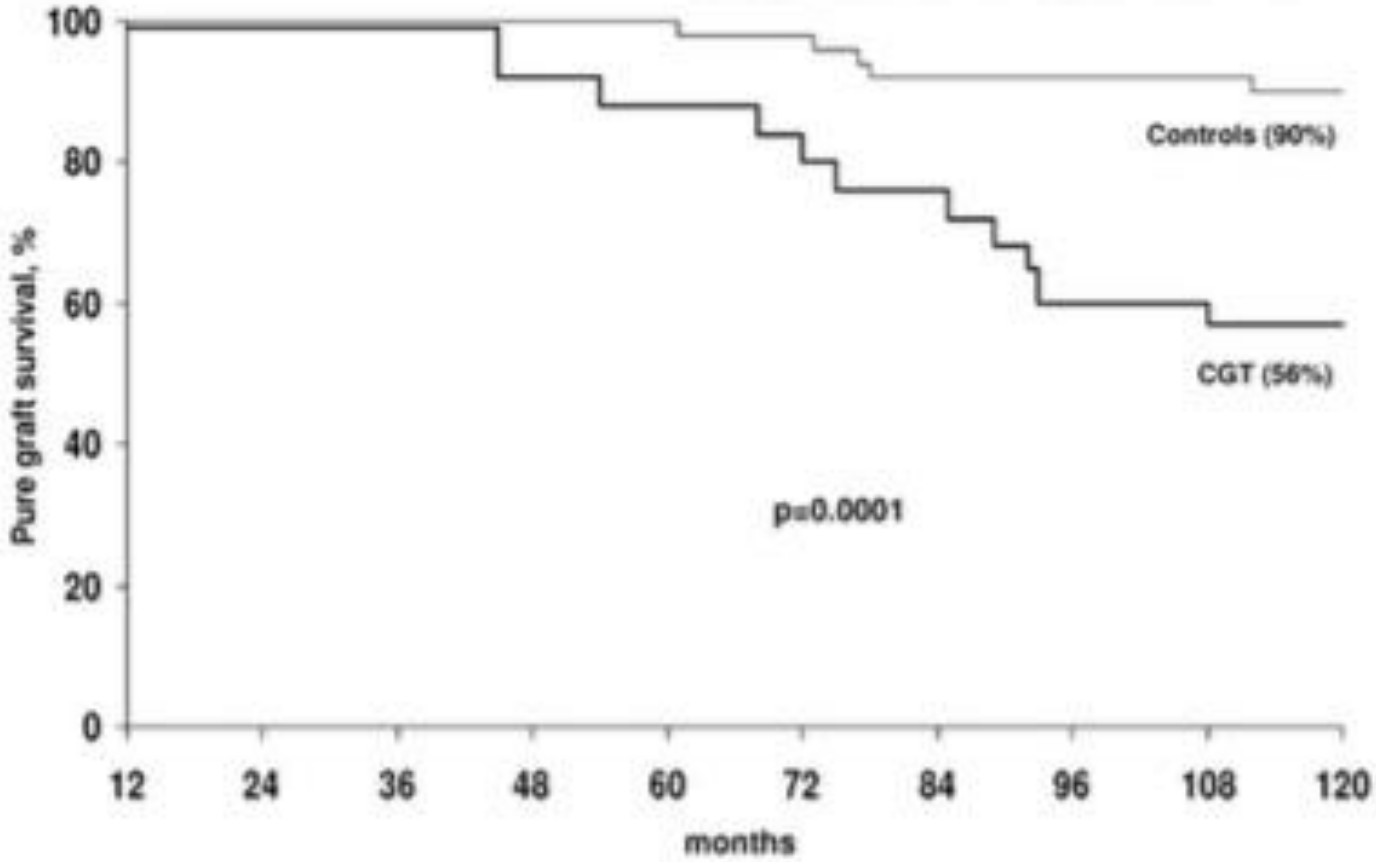


FIGURE 2. Pure graft survival excluding death in patients with TGP vs controls.

Banfi G et al., Transplantation, 2005

DSA impacts on outcome

Table 1: Comparison of HLA-sensitized kidney transplant recipients and nonsensitized match control subjects*

	p-Value
Age (ye	0.69[1]
Gender	1.0[1]
Ethnicit	0.82[1]
Retrans	0.002[1]
ABDR r	0.005[1]
Preemp	< 0.001[1]
Dialysis	< 0.001[1]
Living d	1.0[1]
Living-r	0.37[1]
Primary	
Diabete	0.002[1]
Polycys	0.33[1]
AHGCD	0.18[2]
CDC ne	0.02[2]
CDC po	
TFXM c	0.001[2]
BFXM c	0.239[2]
Class I	n/a
Class II	
Class I	
Baselin	0.002[2]
Baselin	< 0.001[2]
Follow-u	< 0.001[1]
Donor g	0.33[1]
Donor a	0.26[1]

Data ar

[1]The re

[2]p value II only or class I and II).

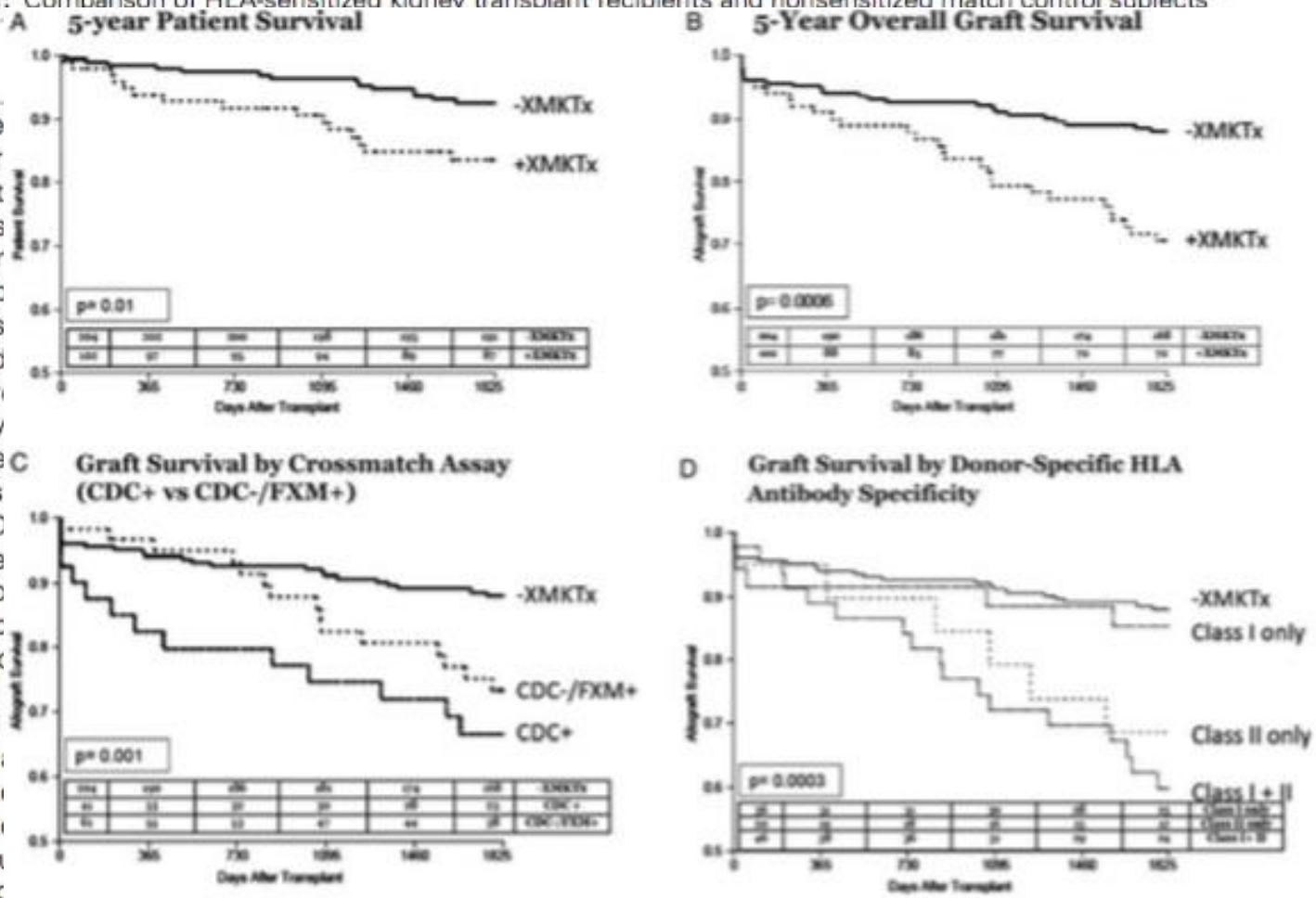


Figure 1: Five-year outcomes after positive crossmatch live donor kidney transplant (+XMKTx). Actual 5-year outcomes are shown for +XMKTx including patient survival (panel A); overall death-censored graft survival (panel B); grafts survival by baseline crossmatch assay type (+XMKTx recipients who were 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.

Bentall A. et al., AJT, 2013

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 *dn*DSA development: Total cohort

Total Cohort	DR *dn*DSA *n*=596, 29 Events		DQ *dn*DSA *n*=596, 51 Events		DR or DQ *dn*DSA *n*=596, 66 Events	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Recipient age at transplant, yr	0.97 (0.95 to 0.99)	0.02	0.97 (0.95 to 0.98)	0.002	0.97 (0.96 to 0.99)	0.001
Nonadherence	3.07 (1.40 to 6.52)	<0.01	3.11 (1.71 to 5.58)	<0.001	3.09 (1.83 to 5.15)	<0.001
Cyclosporin versus tacrolimus	2.14 (0.93 to 4.70)	0.07	1.97 (1.06 to 3.52)	0.03	2.28 (1.35 to 3.78)	0.002
HLA-DR$\beta_{1/3/4/5}$ eplet mismatch/ten mismatches	2.79 (1.84 to 4.27)	<0.001				
HLA-DQα_1/β_1 eplet mismatch/ten mismatches			2.00 (1.52 to 2.67)	<0.001		
HLA-DR$\beta_{1/3/4/5}$ + HLA-DQα_1/β_1 eplet mismatch/ten mismatches					1.37 (1.18 to 1.58)	<0.001

Wiebe C. et al., JASN, 2017

Personalized approach based on EPLET?

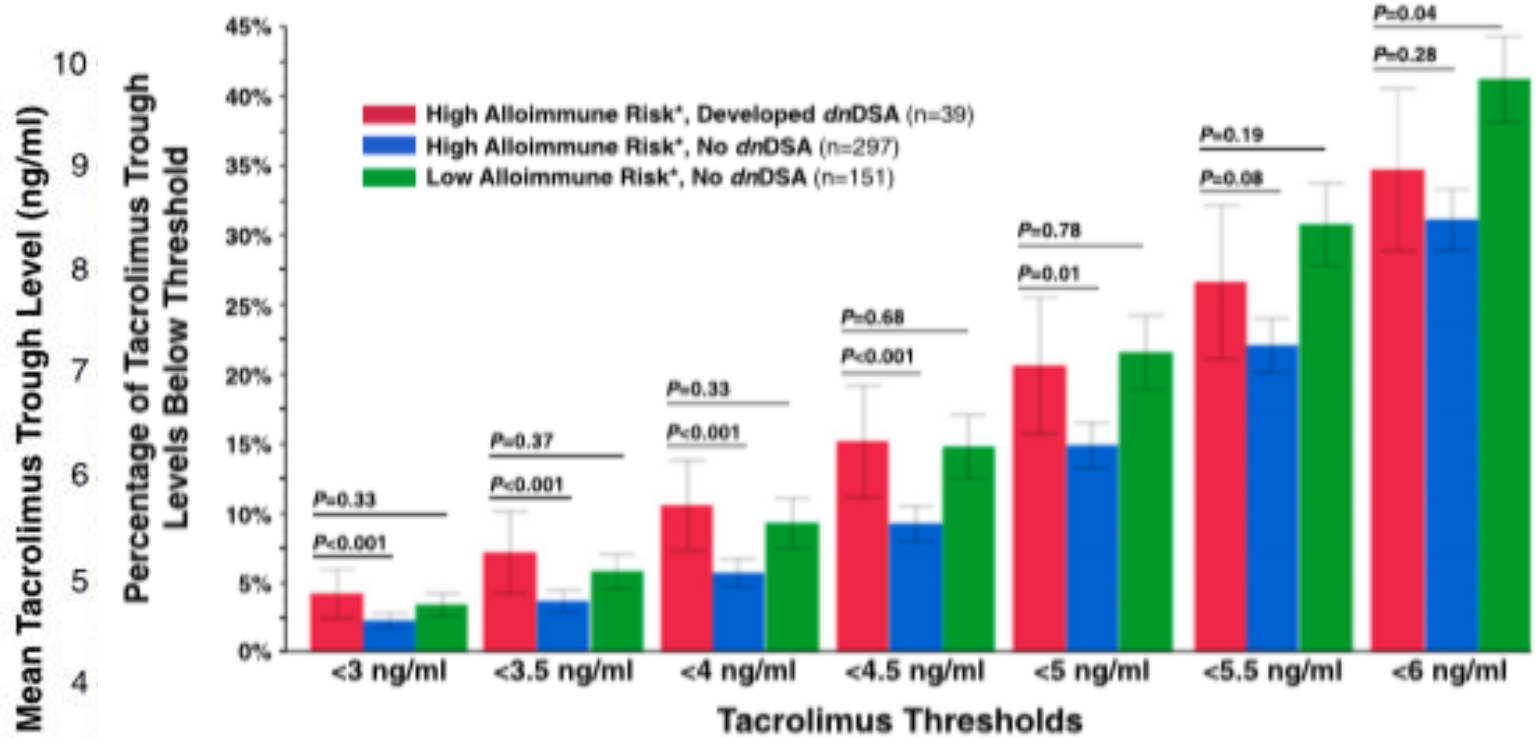
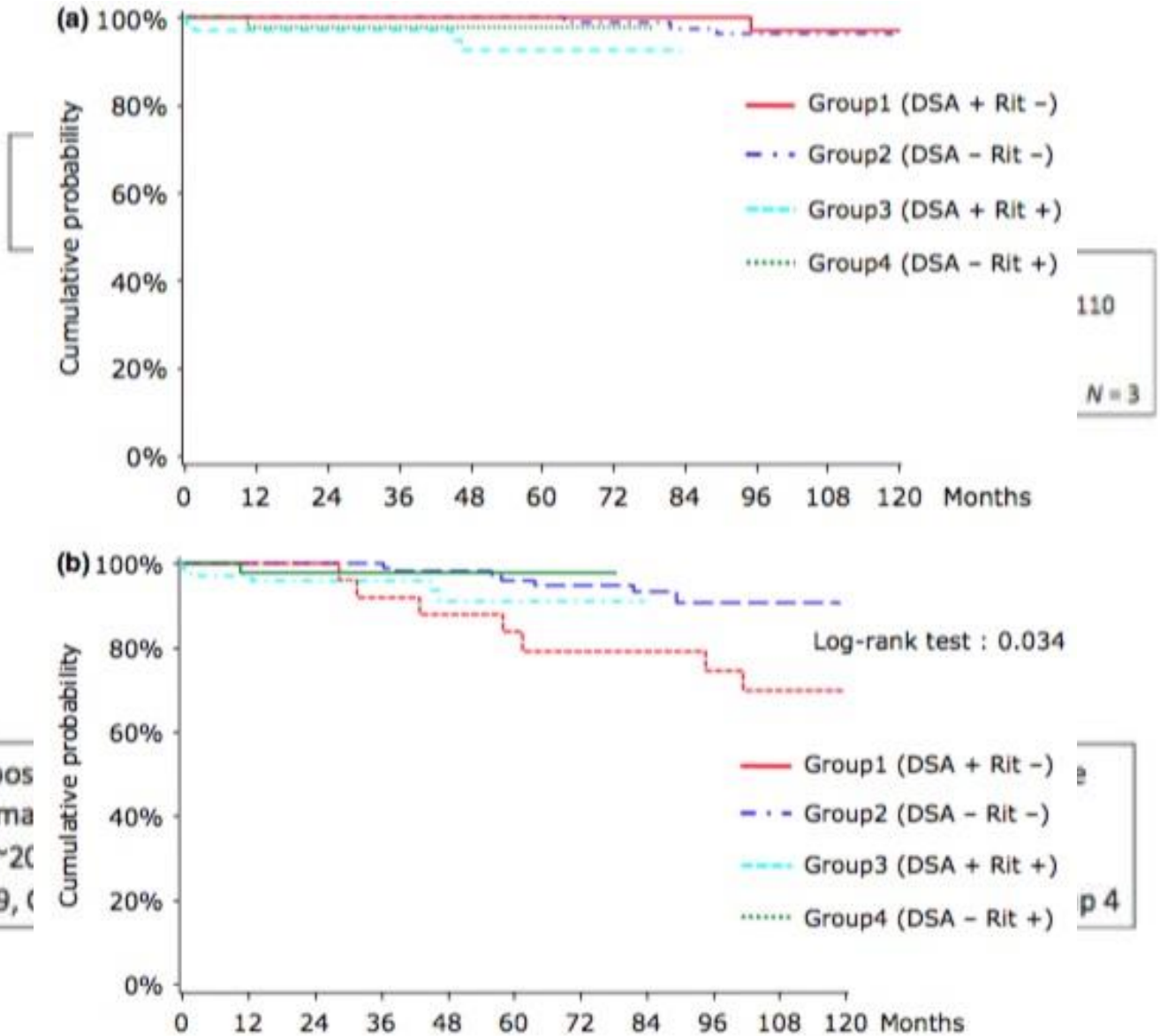


Figure 6. Eplet mismatch modulates the effect of tacrolimus trough levels on the development of *dn*DSA. High risk: HLA-DR or -DQ eplet mismatch >11; low risk: HLA-DR and -DQ eplet mismatch ≤11. *P* values represent a comparison of high-risk patients who developed *dn*DSA with high-risk patients who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

Wiebe C. et al., JASN, 2017

Rituximab

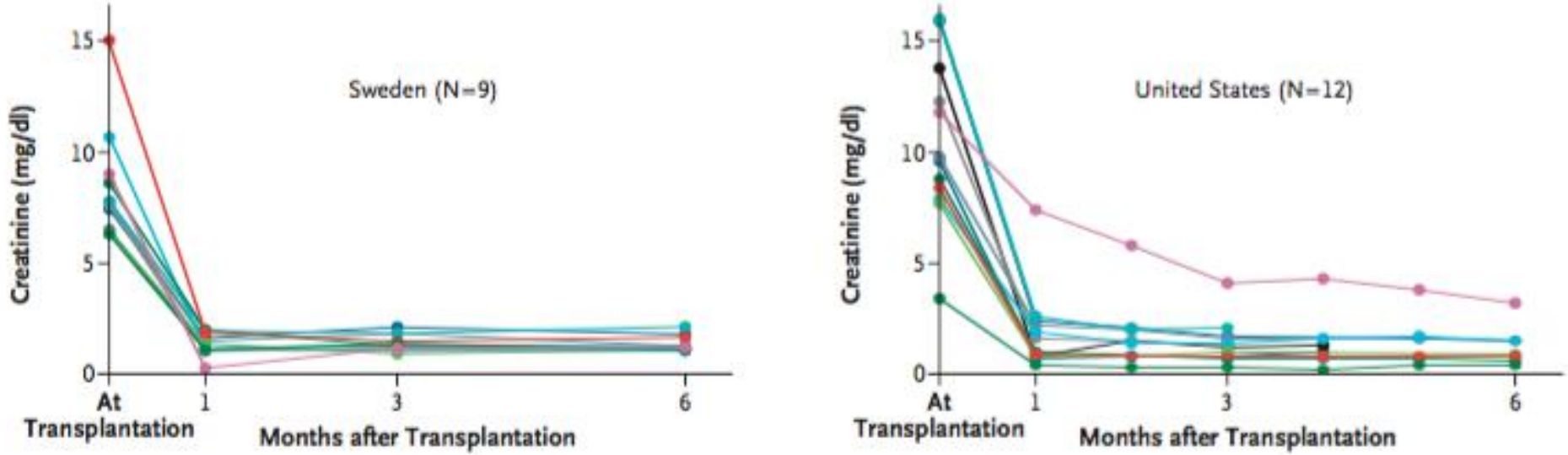


Ishida H. et al., Transpl Int, 2014

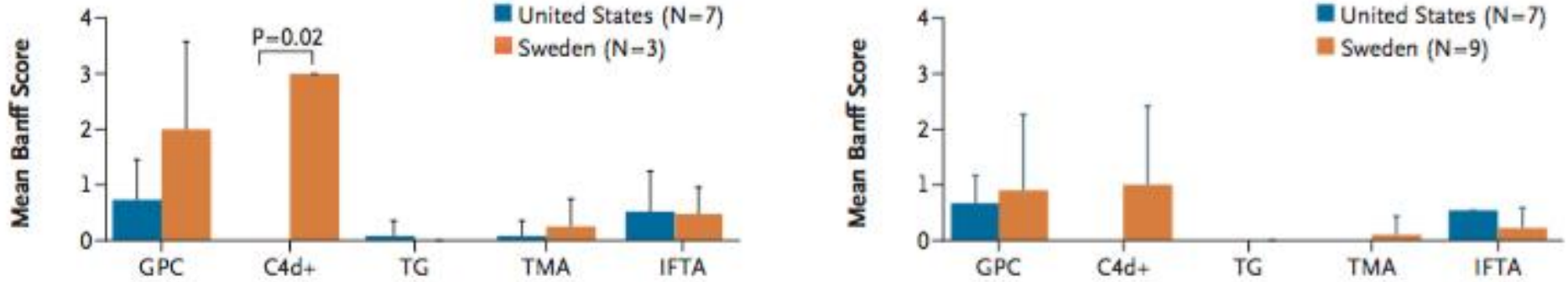
IgG endopeptidase?

A HLA-Antibody Levels before and 6 Hr after Treatment

B Serum Creatinine Levels



C Scoring of Biopsy Results



Results of Biopsy for Antibody-Mediated Rejection, According to Banff Criteria

Per-Protocol Biopsy Results, According to Banff Criteria

shows a similar analysis of the C1q-binding HLA antibodies (results are from the C1qScreen single-antigen assay). Complete or near-complete elimination of C1q binding was observed in samples obtained 1 hour after treatment.

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