Treatment of antibody-mediated rejection with eculizumab

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Diagnostic criteria for AMR

C4d-Positive ABMR

Serologic Evidence
- DSA present

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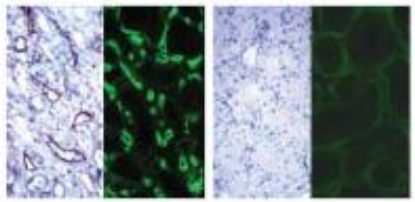
Immunopathologic Evidence
- IF: Diffuse-positive C4d in PTC
- IHC: Diffuse- or focal-positive C4d in PTC



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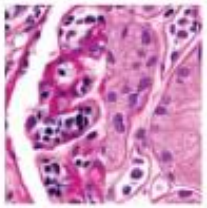
Histopathologic Evidence ACUTE
- ATN like changes, and/or
- Peritubular capillaritis, and/or
- Glomerulitis, and/or
- Arterial fibroid necrosis, and,
- No evidence for chronic capillary injury (reduction and/or multilayering of glomerular and peritubular capillary basement membranes)



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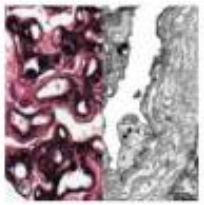
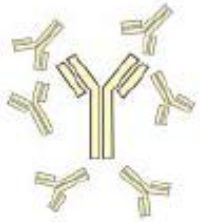
Histopathologic Evidence CHRONIC
- Transplant glomerulopathy, and/or
- PTC basement membrance multilamination, and/or
- IFTA, and/or
- Fibrous intimal thickening of arteries
- May be accompanied by glomerulitis and/or capillaritis





C4d-Negative ABMR

Proposed criteria under discussion by Banff working group

Serologic Evidence
- DSA present

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Immunopathologic Evidence
- Negative C4d staining; and
- Endothelial activation, detected by increased mRNA expression of endothelial genes, such as W/F, PECAM, SELE, etc; and/or
- Evidence for glomerular and/or capillary endothelial cycling (CD31+KI67+ cells lining the microcirculation)

+

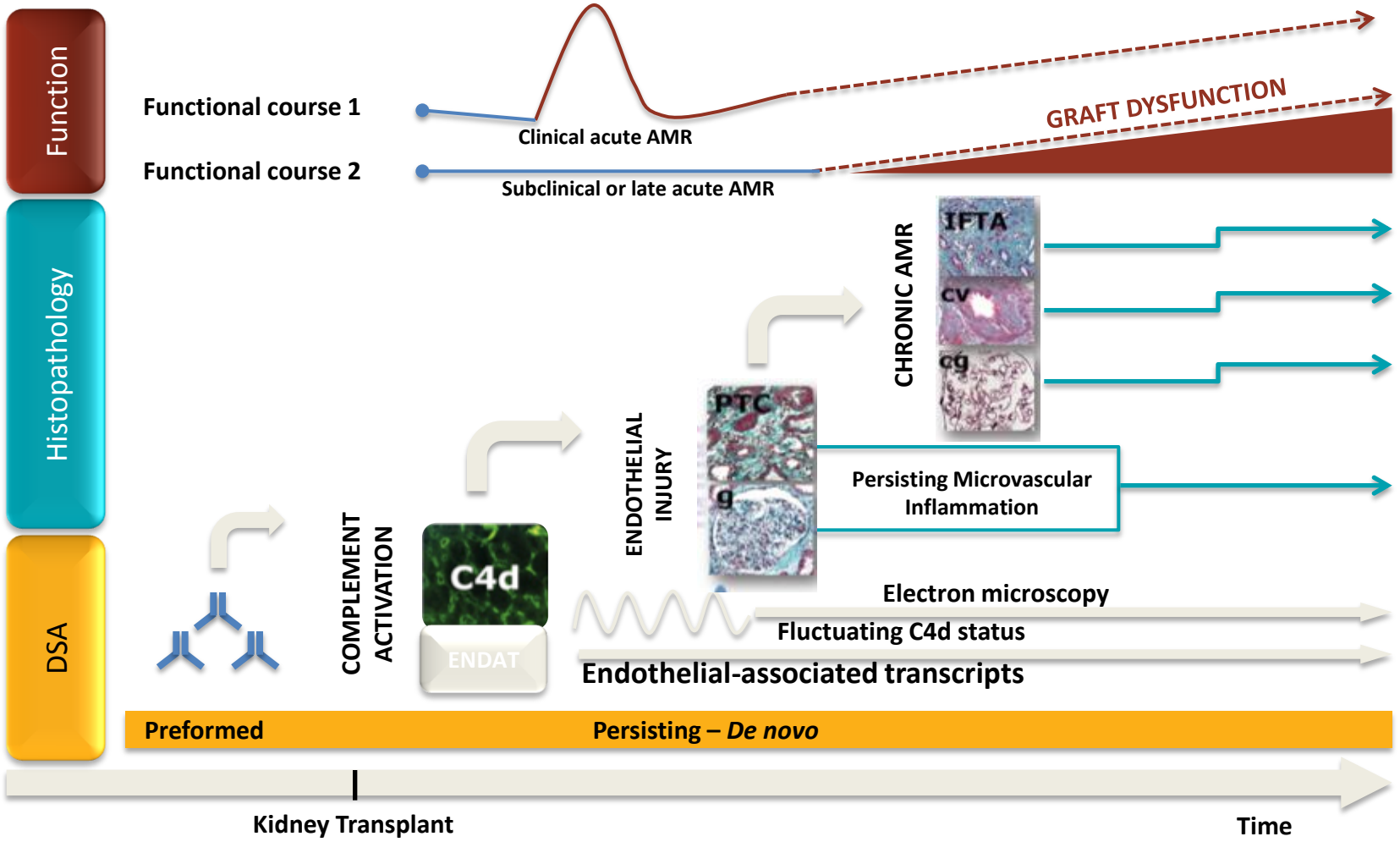
Histopathologic Evidence ACUTE
- Peritubular capillaritis, and/or
- Glomerulitis, and/or
- Thrombotic microangiopathy, and/or
- Arterial fibroid necrosis, and
- No evidence for chronic capillary injury (reduction and/or multilayering of glomerular and peritubular capillary basement)

+

Histopathologic Evidence CHRONIC
- Transplant glomerulopathy, and/or
- PTC basement membrane multilamination, and/or
- Fibrous intimal thickening of arteries
- May be accompanied by glomerulitis and/or capillaritis

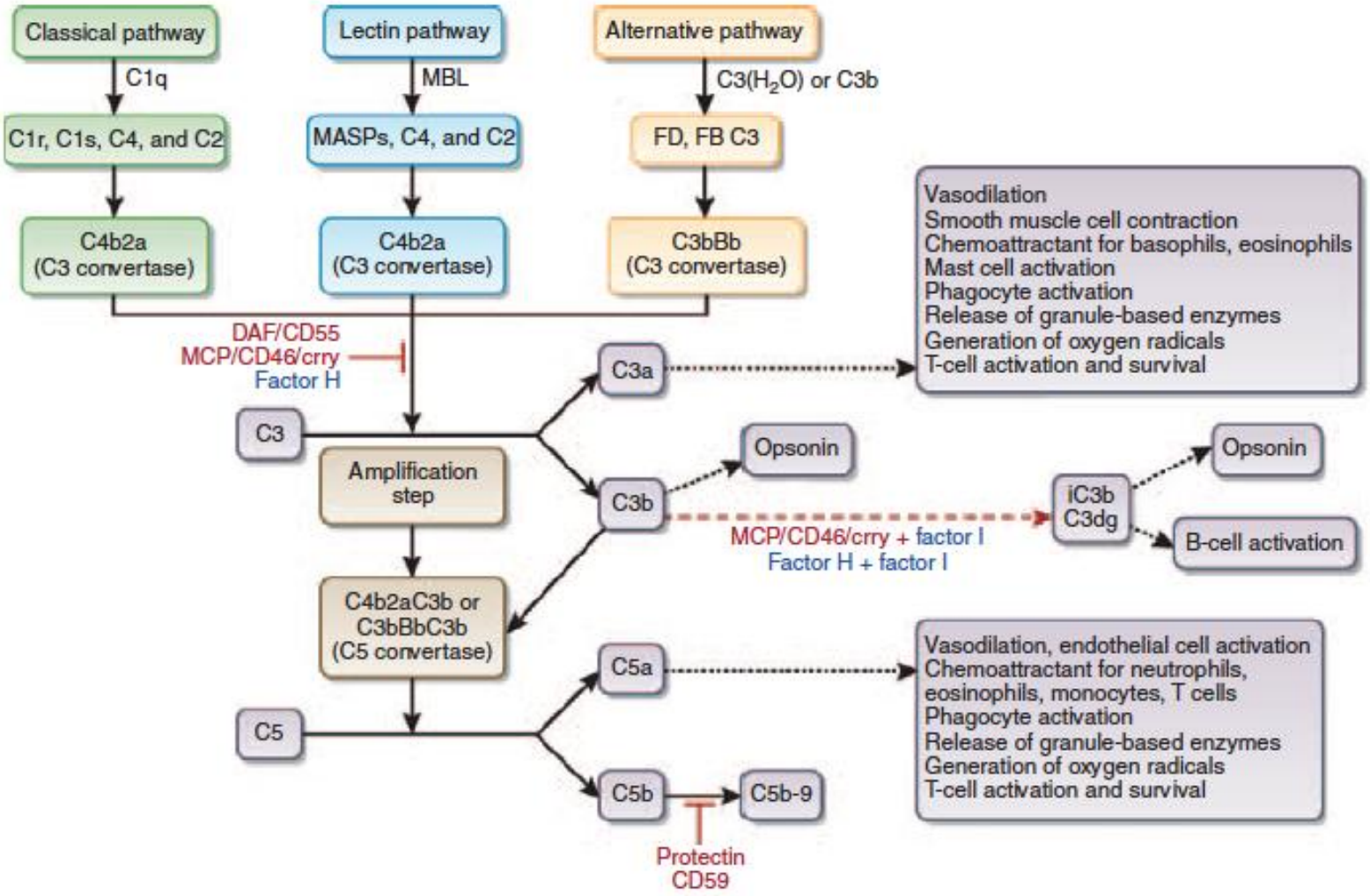
Djamali et al, AJT 2014

Antibody-mediated allograft damage



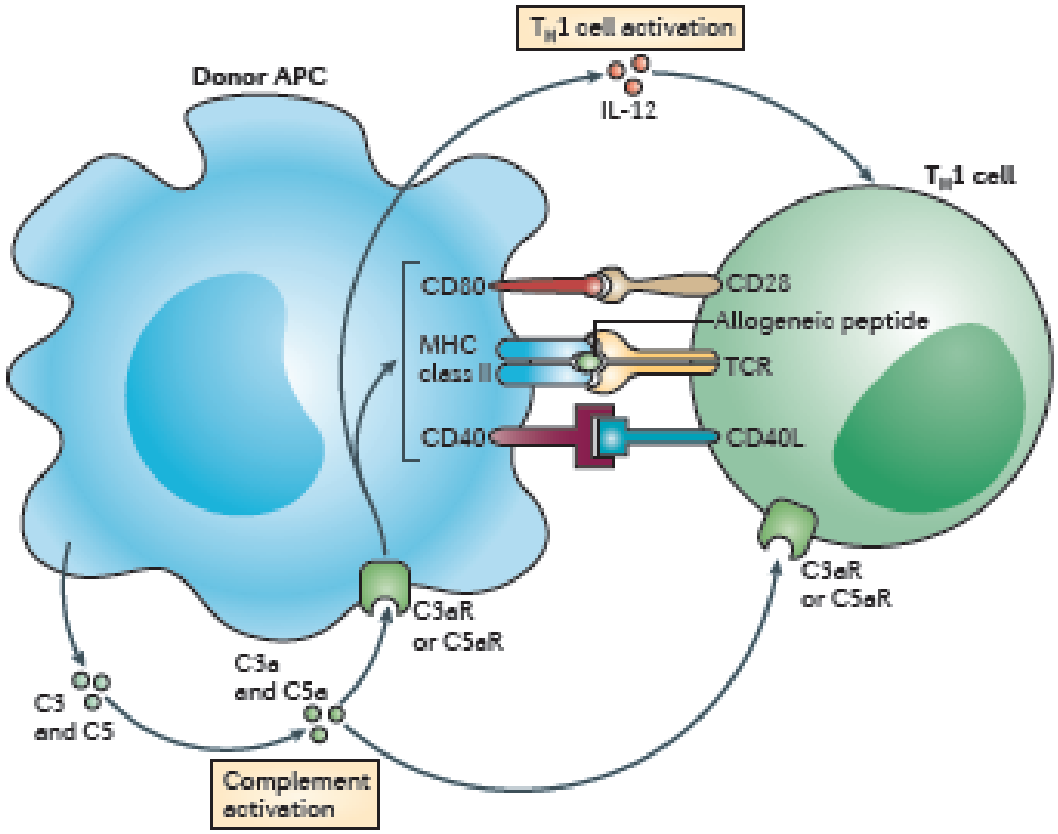
Loupy A, et al. *Nat Rev Nephrol*. 2012;8:348–357.

Complement cascade



Vieyra&Heeger, KI 2010

Complement can induce T-cell priming



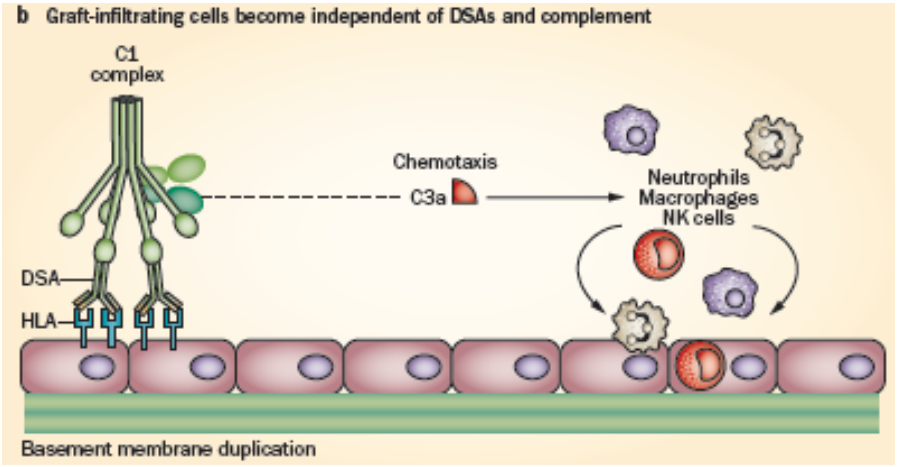
C3aR and C5aR signalling skews the differentiation of naive CD4+ T cells towards TH1

→ Increases alloAg presentation

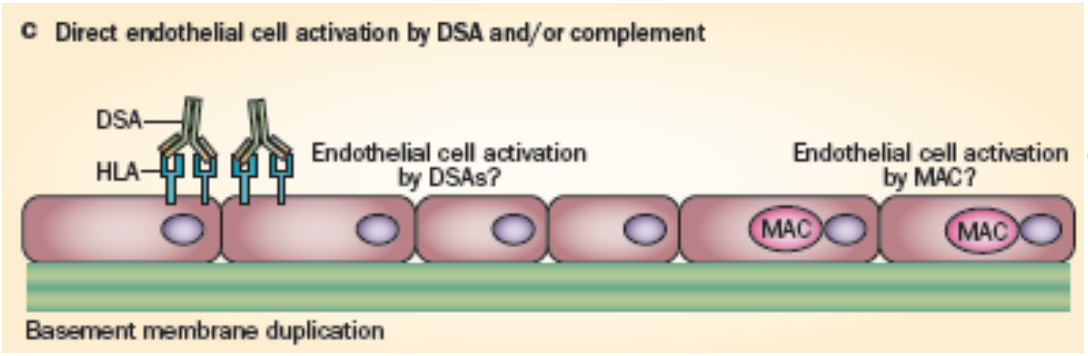
→ Increases expression of co-stimulatory molecules (CD80 & CD40)

Vieyra&Heeger, KI 2010

DSA can induce damage without complement activation



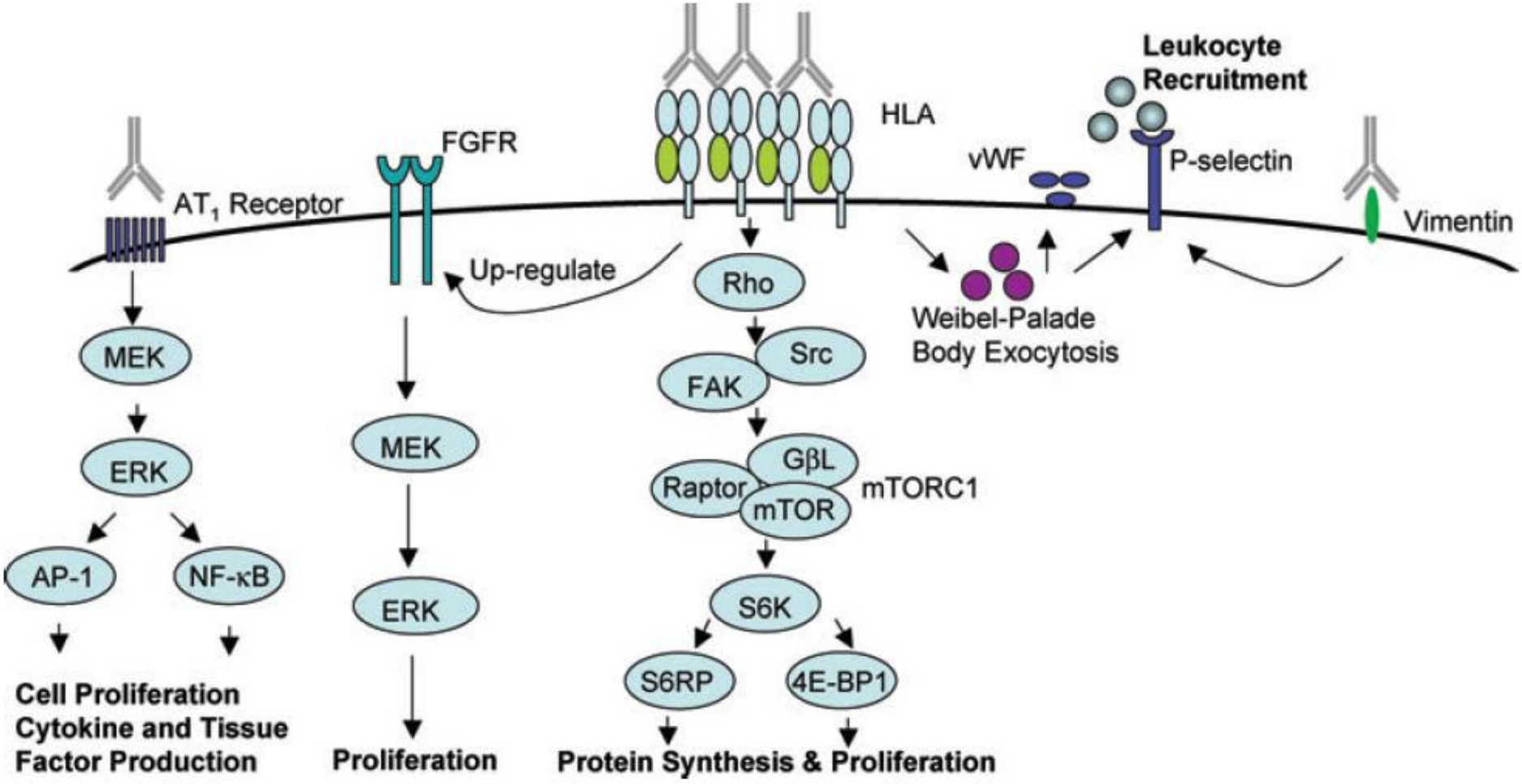
→ Intermitent or low level DSA might lead to TG in absence of C4d deposition and low inflammation



→ DSAs might cause damage independent of complement via direct activation of ECs promoting TG

Stegall M et al Nat Rev 2012

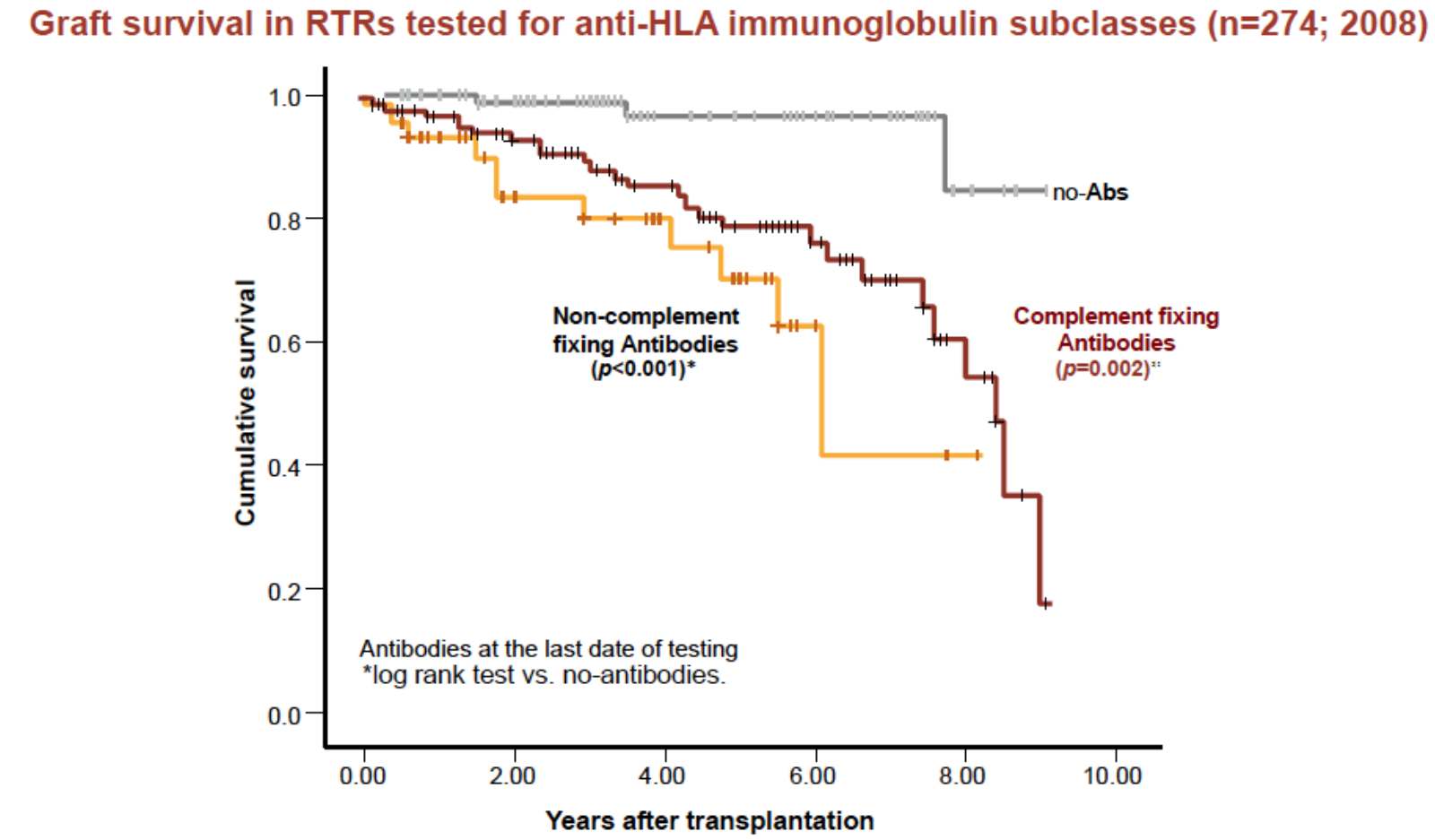
DSA can induce damage without complement activation



Signaling pathways regulating antibody-mediated activation of endothelial cells

Zhang&Reed, AJT 2009

DSA can induce damage without complement activation



Arnold ML et al. *Transplant International* 2014;27:253-261.

A pathogenic view of AMR

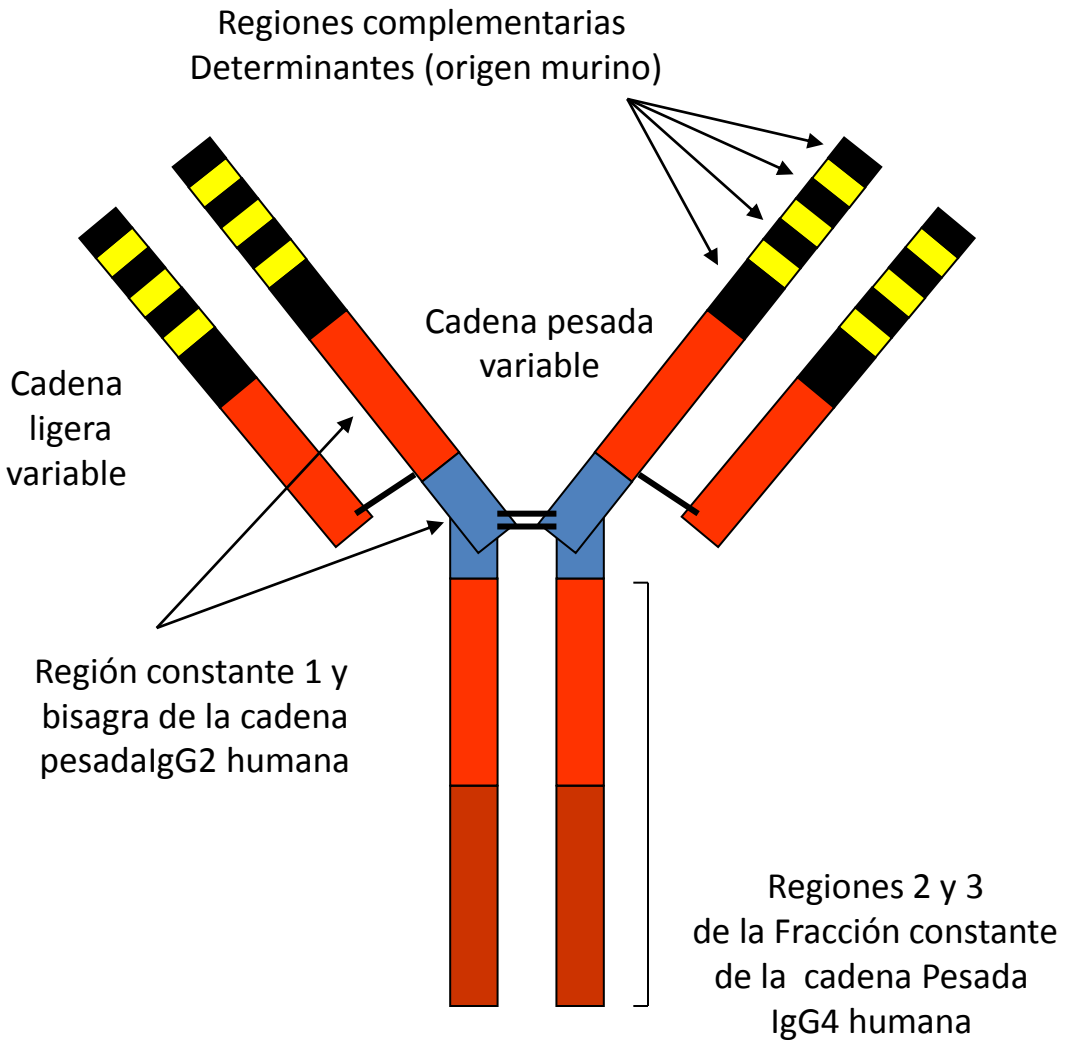
- H-AMR:
  - Preformed antibodies against donor-antigens CDC+
- A-AMR:
  - Previous antigen exposure
  - Pre-transplant DSA or memory B-cell
  - Severe complement activation
- SC/C-AMR
  - DSA persistence of de novo
  - Low-intensity complement activation
  - Complement-independent DSA pathogenic mechanisms

Eculizumab in AMR

- **a-AMR prophylaxis**
- **a-AMR treatment**

- sc-AMR and c-AMR

Eculizumab (Soliris®)



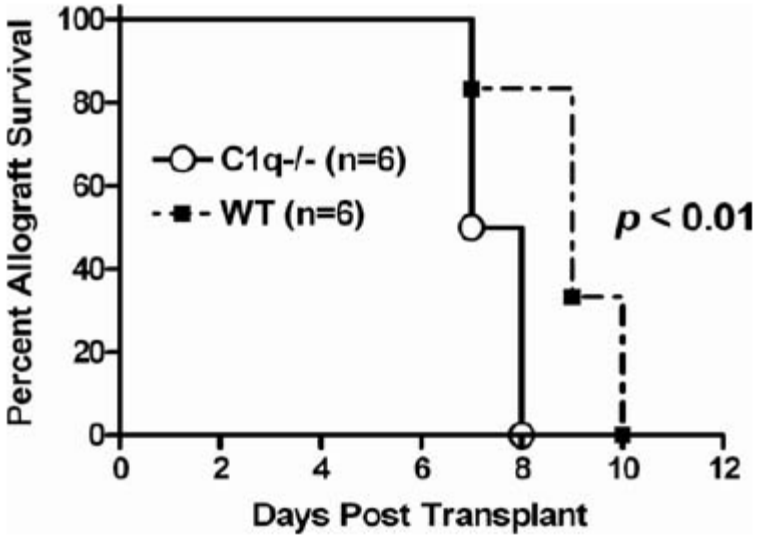
Eculizumab está diseñado para reducir la inmunogenicidad y eliminar las funciones efectoras:

- Adición de regiones determinantes complementarias murinas entre las secuencias estructurales de las cadenas pesadas y ligeras humanas.
- Combinación de secuencias humanas de cadenas pesadas IgG2 e IgG4 para formar una región constante híbrida incapaz de unirse a receptores Fc o de activar la cascada del complemento.

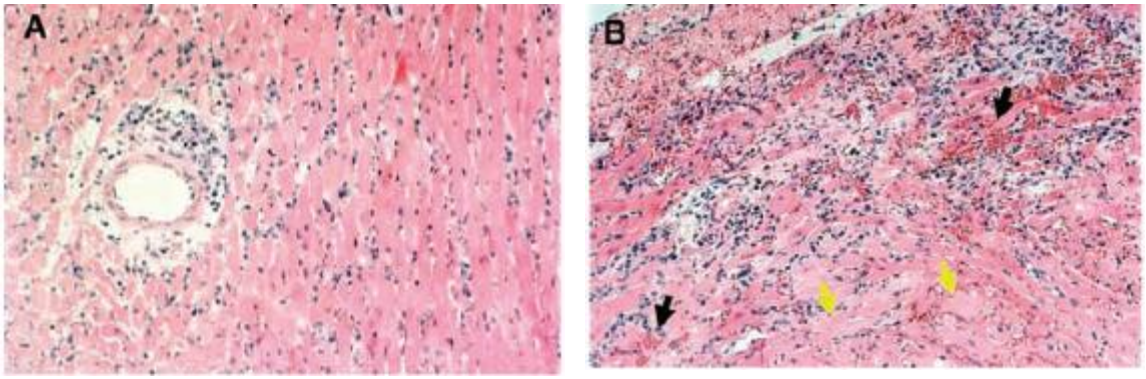
Eculizumab tiene así una alta afinidad para C5 humano, bloqueando eficazmente su activación, la secuencia proinflamatoria y sus propiedades citolíticas.

Rother et al. Nature Biothechnol. 2005; 11: 1258.

C1q deficiency does not delay allograft rejection

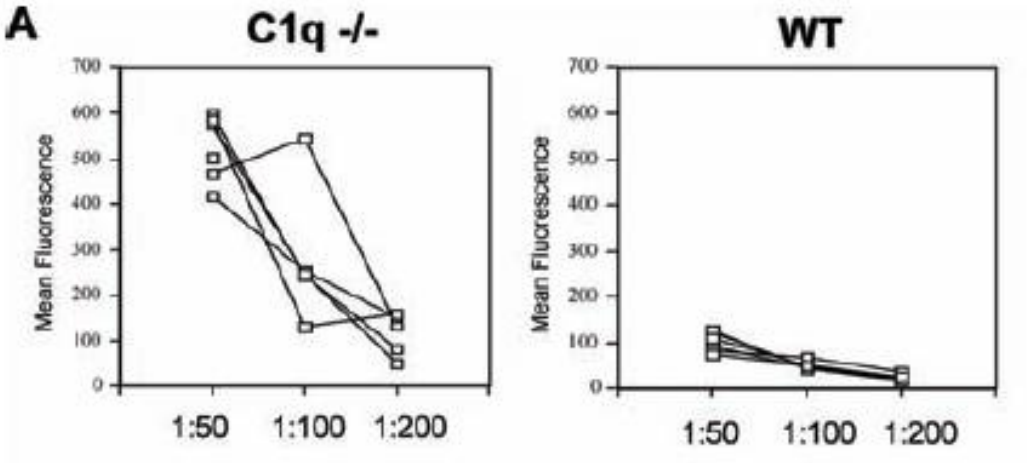


C1q deficiency exacerbates pathology of rejection

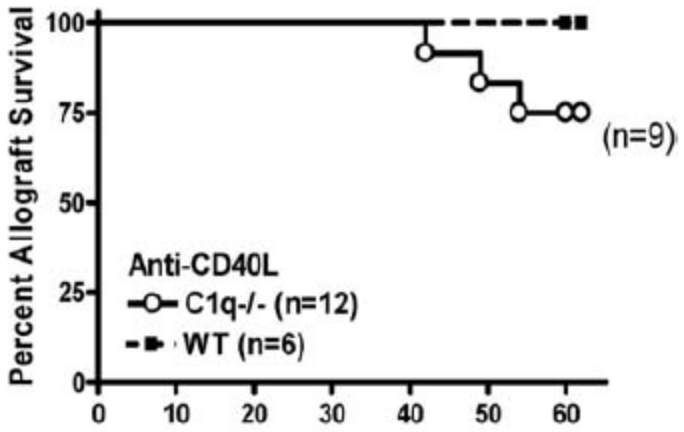


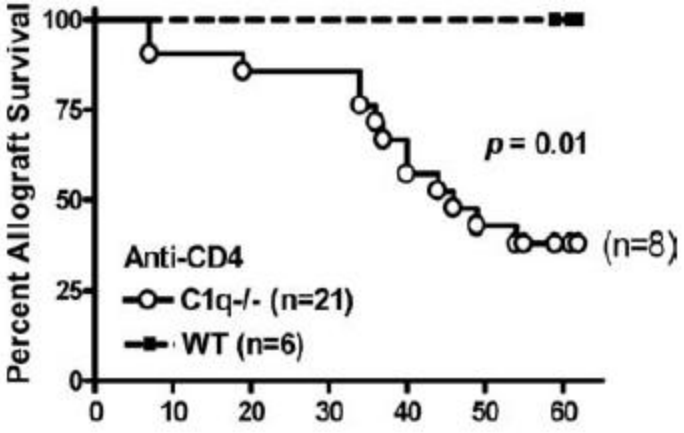
Csencsits et al, AJT 2008

C1q deficiency accelerates production of donor-reactive IgG



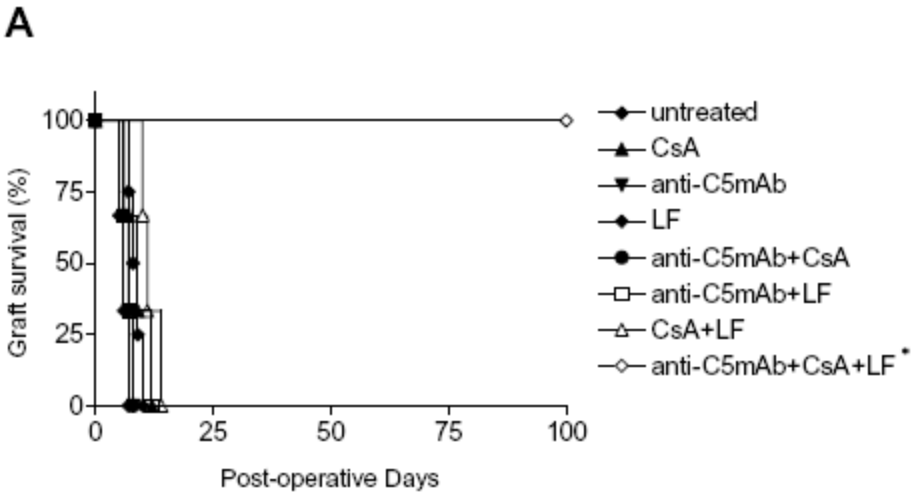
Classical complement pathway is needed to graft acceptance

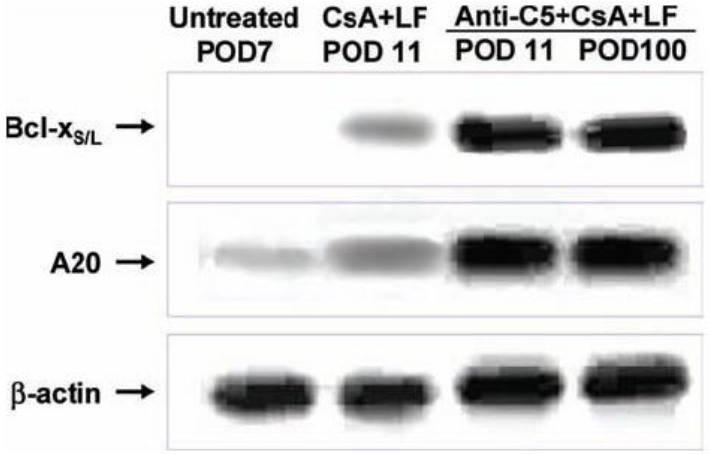




Csencsits et al, AJT 2008

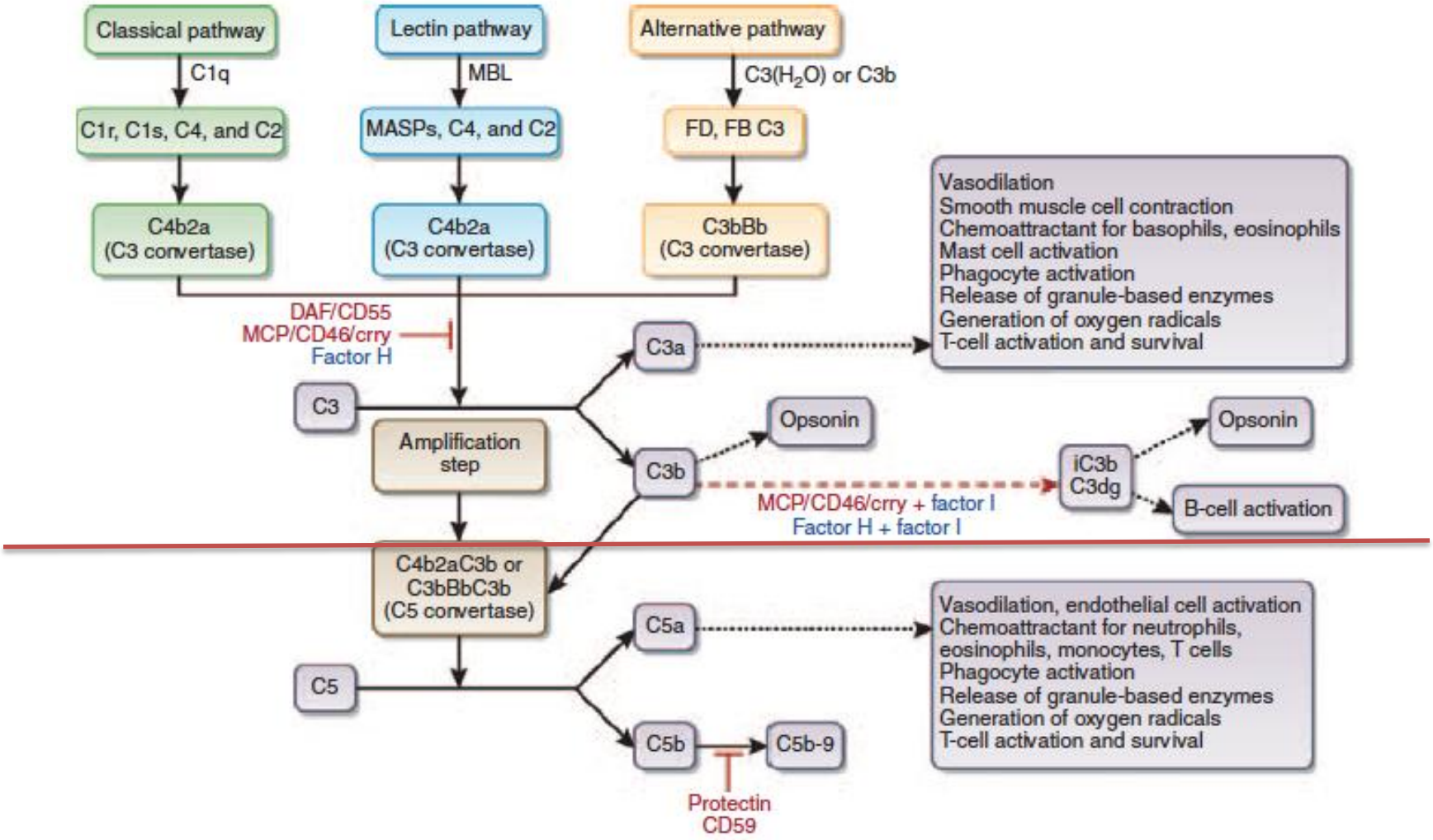
C5 Blockade with Conventional Immunosuppression Induces Long-Term Graft Survival in Presensitized Recipients





Rother et al, AJT 2008

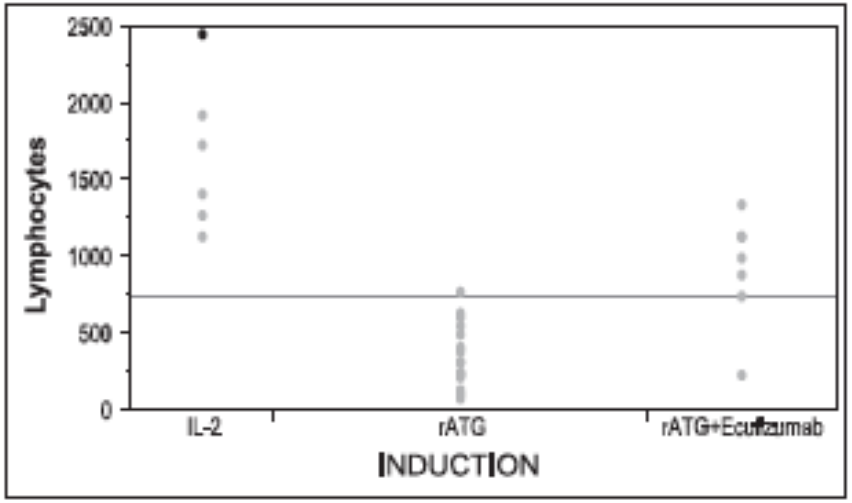
C3b formation may amplify B-cell activation



Vieyra&Heeger, KI 2010

Peripheral T cells are depleted by rATG in the presence of Eculizumab

Month 1 after TX

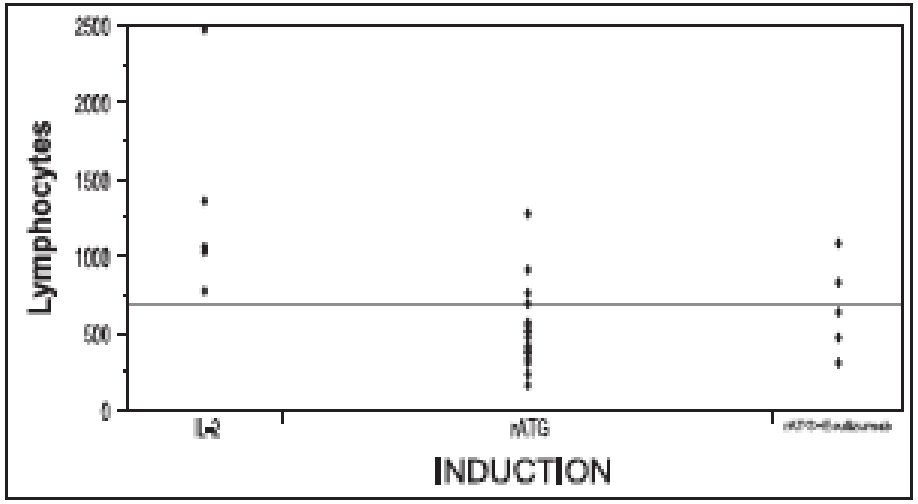


P [0.0005 | 0.016]

P [>0.01]

P (3-Group Comparison) 0.0002

Month 3 after TX



P [0.001 | 0.37]

P [0.08]

P (3-Group Comparison) = 0.004

Goh B K et al Tranplant Immunol 2012

American Journal of Transplantation 2011; 11: 2405–2413
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03757.x

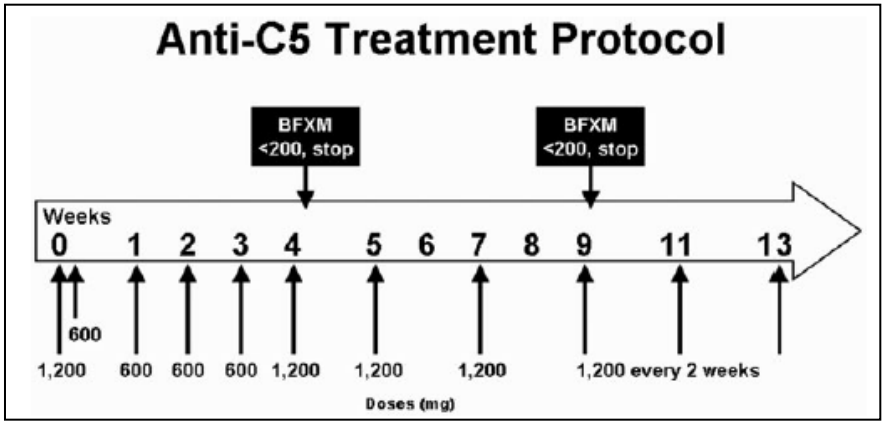
Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients

M. D. Stegall[a,*], T. Diwan[a], S. Raghavaiah[a], L. D. Cornell[b], J. Burns[a,c], P. G. Dean[a], F. G. Cosio[d], M. J. Gandhi[b], W. Kremers[e] and J. M. Gloor[d]

Key words: Alloantibodies, anti-HLA antibodies, antibody-mediated rejection, complement, chronic rejection, kidney transplantation, sensitized recipients

→ Prevention of ABMR in Sensitized patients (POS BFXM) pre-TX >200 <450

(Comparison with an historical cohort group not treated with eculizumab)



Main Clinical Outcome

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

Category	Eculizumab group (n = 26)	Control group (n = 51)	p-Value
Follow-up	11.8 ± 6.3	48.8 ± 14.1	
(mean months ± SD, range)	(3.0–27.5)	(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.

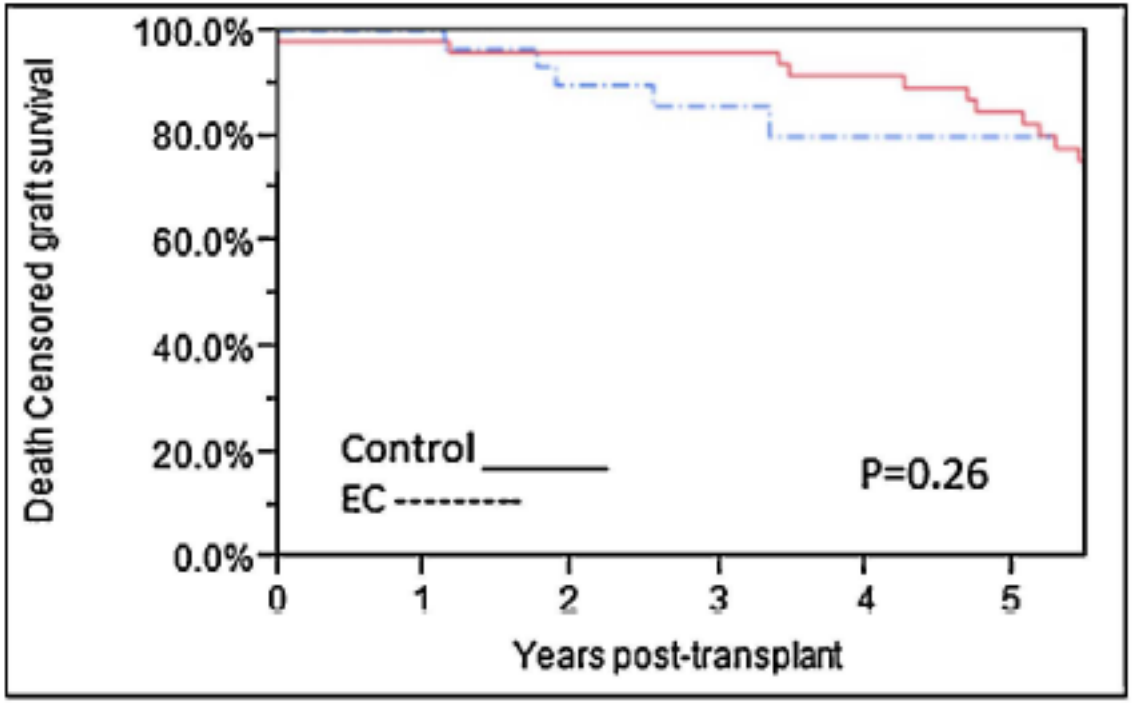
→ C5 inhibition prevented ABMR despite high levels of DSAs and C4d deposition in the allograft

2 patients with ABMR (day 7) despite eculizumab → C5-independent mechanism ??

Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year

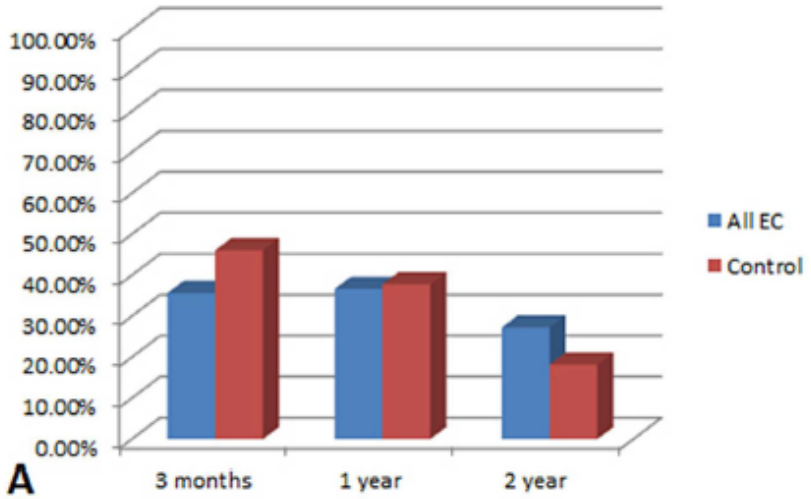
L. D. Cornell[1], C. A. Schinstock[2], M. J. Gandhi[3], W. K. Kremers[2] and M. D. Stegall[2,*]

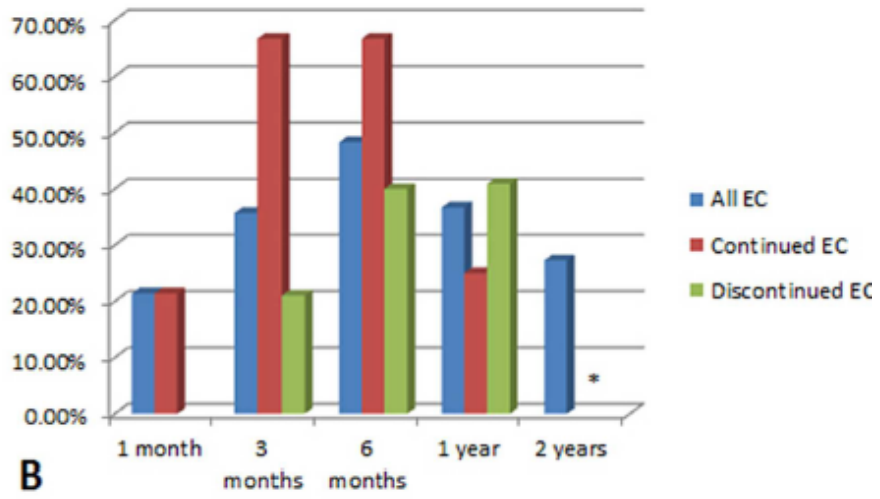
American Journal of Transplantation 2015; XX: 1–10
Wiley Periodicals Inc.



At risk	0	1	2	3	4	5
Control	48	46	46	45	40	37
EC	30	30	26	21	8	2

Subclinical ABMR on protocol biopsies



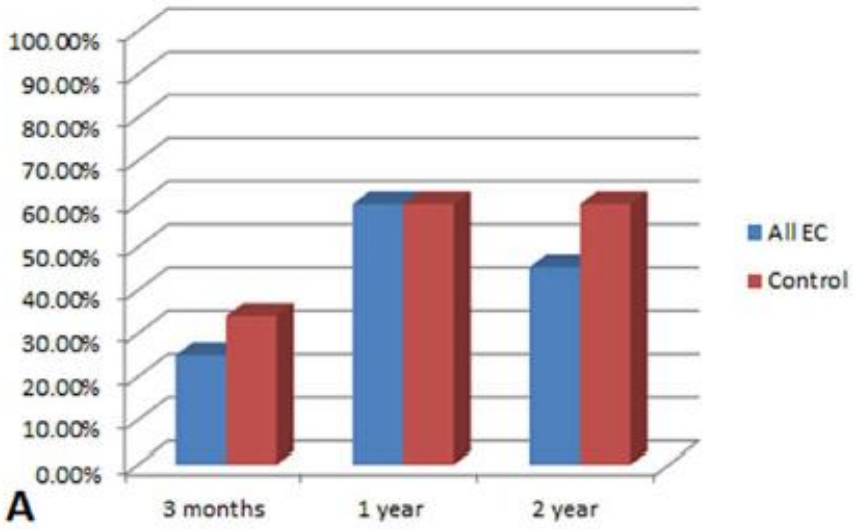


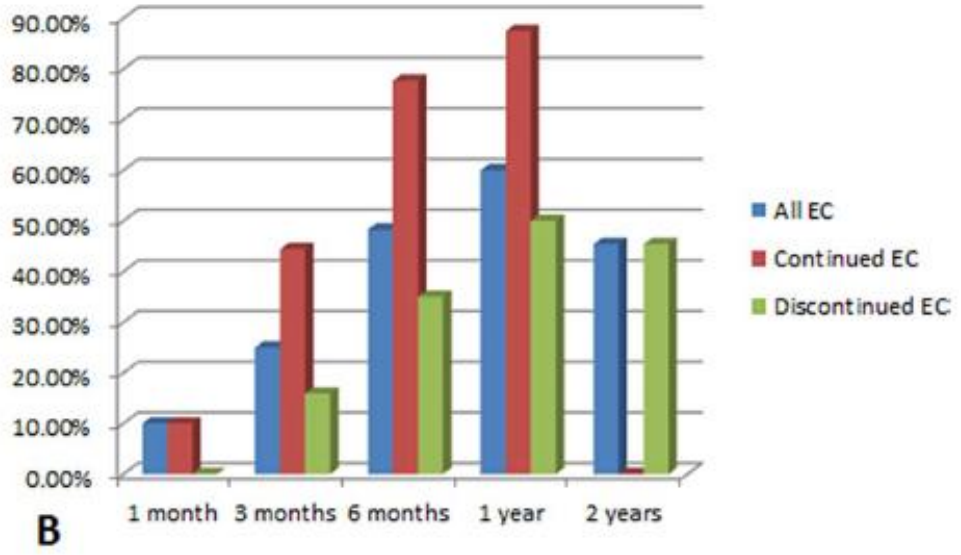
Subclinical ABMR in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	35.7% (10/28)	36.7% (11/30)	27.3% (6/22)
Control	46.2% (18/39)	36.8% (14/38)	15.1% (5/33)
p-value (EC vs. control)	P=0.46	P=1.0	P=0.32

Subclinical ABMR over time in Eculizumab group					
	1 month	3-4 months	6 months	1 year	2 years
All EC	21.4% (6/28)	35.7% (10/28)	48.3% (14/29)	36.7% (11/30)	27.3% (6/22)
Continued EC	21.4% (6/28)	66.7% (6/9)	66.7% (6/9)	25.0% (2/8)	NA
Discontinued EC	NA	21.1% (4/19)	40.0% (8/20)	40.9% (9/22)	NA
p-value	NA	P=0.03	P=0.26	P=0.67	NA

Cornell LD, et al AJT 215

Moderate-to-severe peritubular capillaritis on protocol biopsies

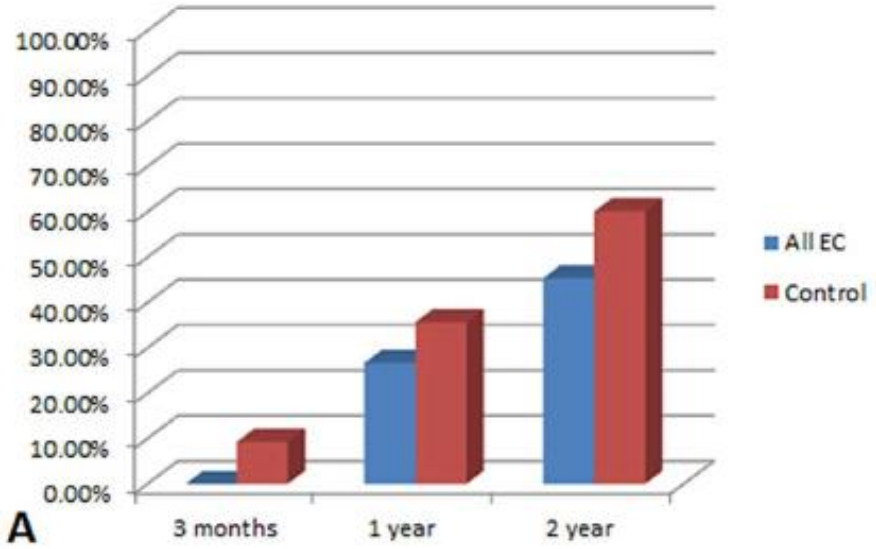


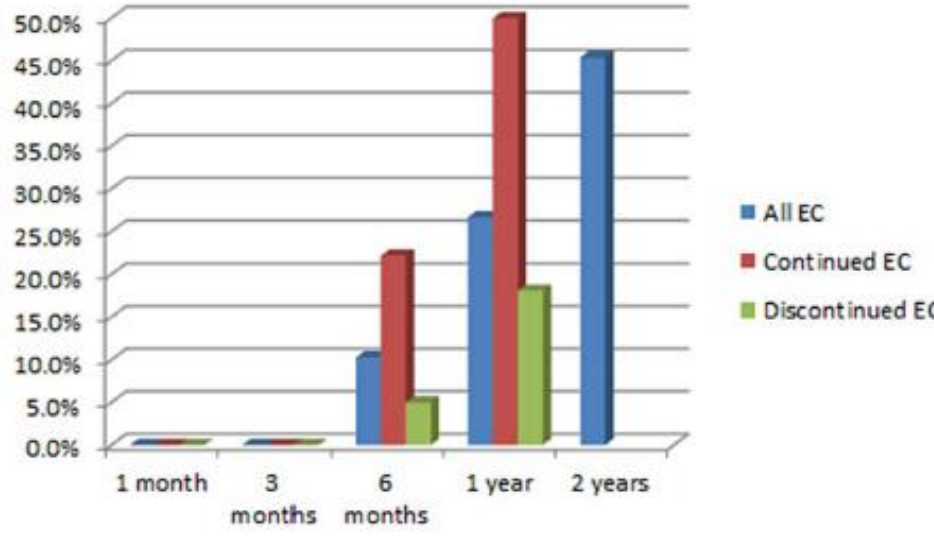


Moderate-to-Severe Peritubular capillaritis in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	25.0% (7/28)	60.0% (18/30)	45.4% (10/22)
Control	34.1% (14/41)	60.0% (21/35)	60.0% (15/25)
p-value (control vs. EC)	P= 0.59	P=1.00	P=0.39

Moderate-to-Severe Peritubular capillaritis over time in Eculizumab group					
	1 month	3-4 months	6 months	1 year	2 years
All EC	10% (3/30)	25.0% (7/28)	48.3% (14/29)	60% (18/30)	45.4% (10/22)
Continued EC	10% (3/30)	44.4% (4/9)	77.7% (7/9)	87.5% (7/8)	NA
Discontinued EC	NA	15.9% (3/19)	35.0% (7/20)	50.0% (11/22)	NA
p-value	NA	P=0.17	P=0.05	P=0.10	NA

Transplant glomerulopathy (chronic ABMR) on protocol biopsies





Transplant Glomerulopathy in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	0% (0/28)	26.7% (8/30)	45.4% (10/22)
Control	9.3% (4/43)	39.5% (15/38)	63.6% (21/33)
p-value (EC vs. control)	P=0.15	P=0.31	P=0.27

Transplant glomerulopathy over time in Eculizumab group					
	1 month	3-4 months	6 months	1 year	2 years
All EC	0% (0/30)	0% (0/28)	10.3% (3/29)	26.7% (8/30)	45.4% (10/22)
Continued EC	0% (0/30)	0% (0/9)	22.2% (2/9)	50.0% (4/8)	NA
Discontinued EC	NA	0% (0/19)	5.0% (1/20)	18.1% (4/22)	NA
p-value	NA	P=1.0	P=0.22	P=0.16	NA

On-going trials with Eculizumab for Prevention of ABMR in Sensitized Kidney Transplantant patients

1. Open-Label, Single-arm, Phase II Study for Prevention of AMR in Sensitized Recipients of Deceased Donor Kidney Transplant **(NCT01567085)**

   Objective → Safety and potential efficacy of eculizumab to prevent ABMR in sensitized **recipients**

2. Open-Label, Randomized, Phase II Study to Prevent AMR in Living Donor Kidney Transplant Recipients Requiring Desensitization **(NCT01399593)**

   Objective → Safety and potential efficacy of eculizumab to prevent ABMR in sensitized recipients

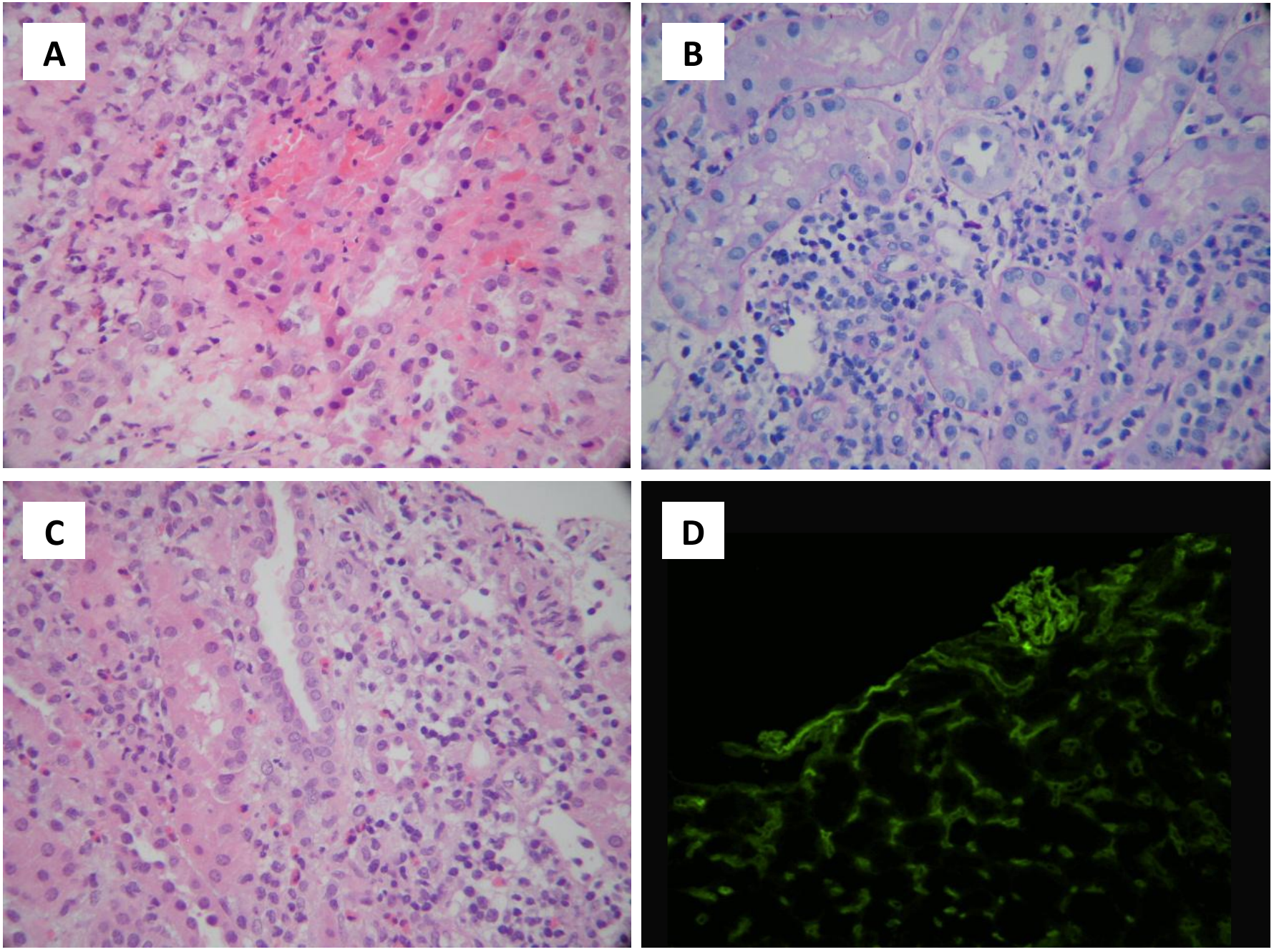
Eculizumab dosing:

-1200mg prior to kidney allograft reperfusion (Day 0)
-900mg on postoperative days 1, 7, 14, 21 and 28
-1200mg on weeks 5, 7 and 9

Eculizumab in AMR

- **a-AMR prophylaxis**
- **a-AMR treatment**

- sc-AMR and c-AMR


A
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C
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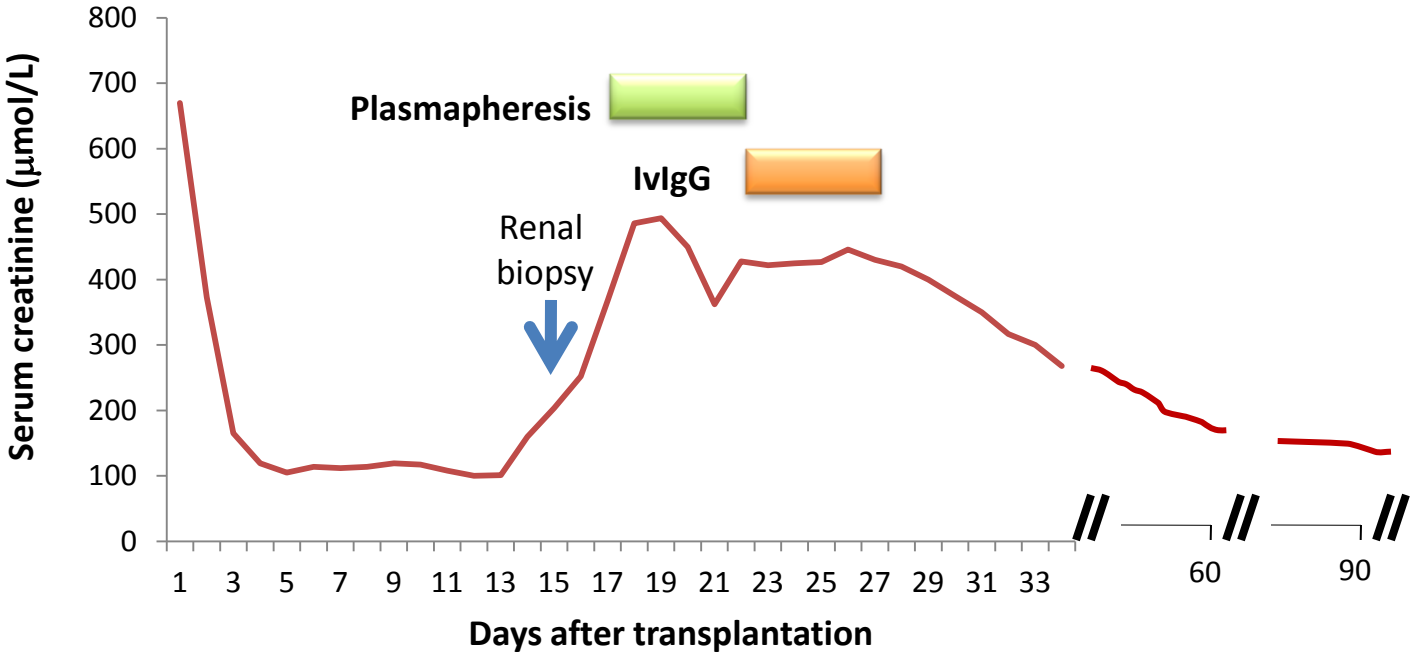
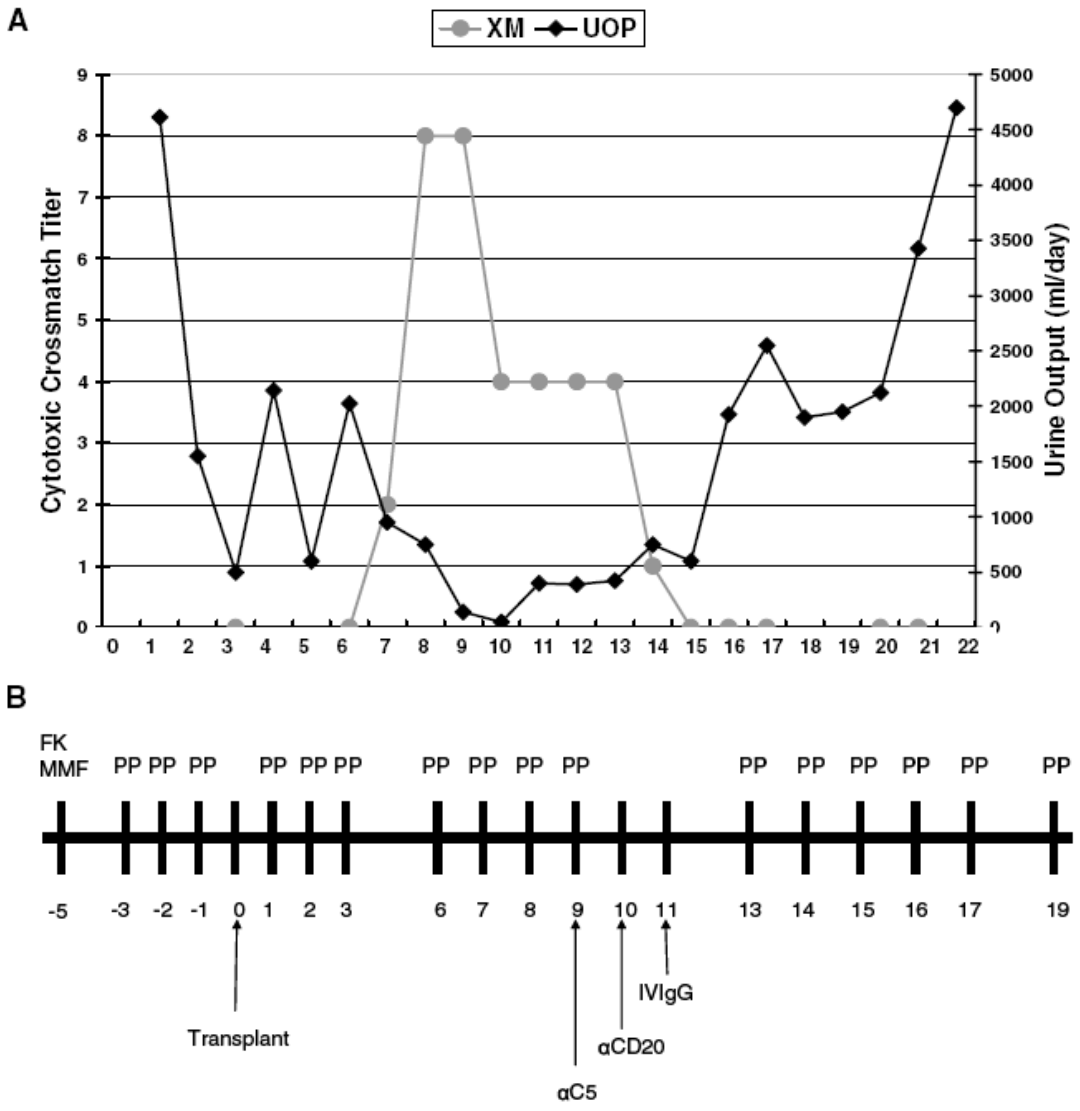
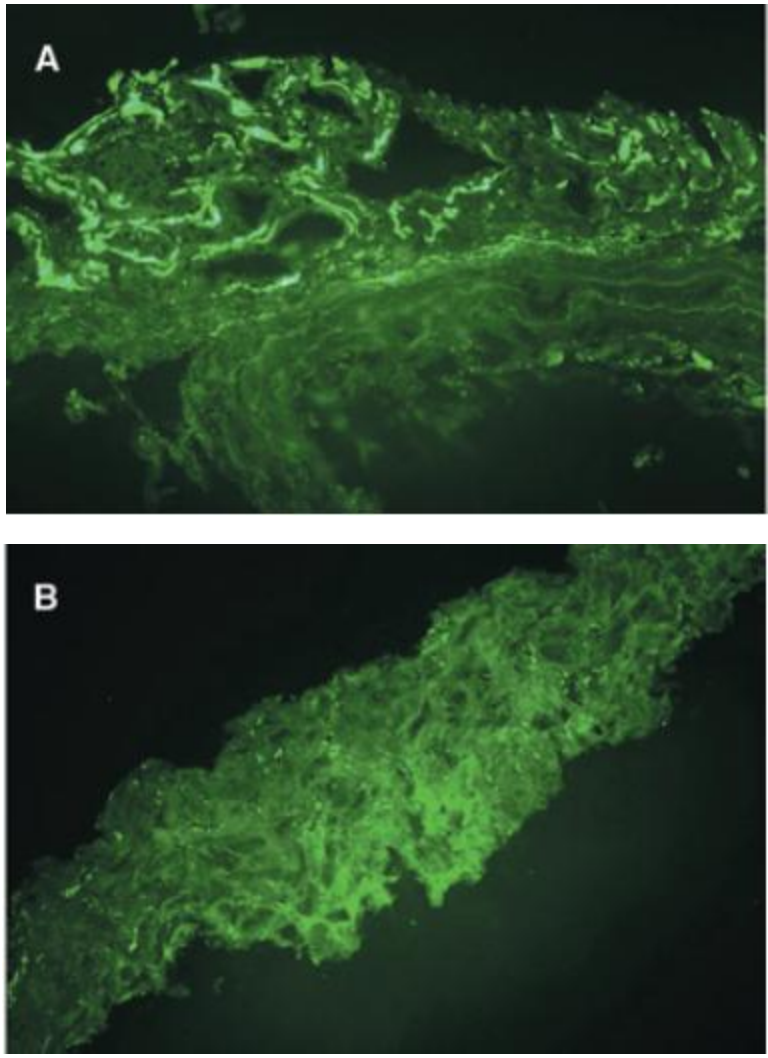
The Bellvitge's protocol for acute ABMR



Cruzado et al, AJT 2009





Locke et al, AJT 2008

Locke et al AJT 2009	Pre-TX DSA class I&II → Desensitization	ABMR	→	Eculizumab + Rxmab
Lonze et al AJT 2010	Pre-TX DSA class I&II → Desensitization	ABMR	→	6-month Eculizumab
Biglarnia et al Tranpl Int 2011	ABOi&Pre-TX DSA class I&II → Desensitizaition	ABO Rejection	→	IA + 2 dose Eculizumab
Chandran et al Transpl Proc 2011	Pre-TX DSA→ desensitization	ABMR / MAT	→	2 doses Eculizumab
Noone et al AJT 2012	Pre-TX DSA and aHUS→ desensitization	ABMR / MAT	→	Eculizumab + Rxmab
Glez-Roncero et al Transpl Proc 2012	Pre-TX DSA → no desensitization	ABMR	→	Eculizumab + Rxmab
	Pre-TX no DSA → no desensitization	ABMR / MAT	→	Eculizumab + Rxmab

Excellent Short-term clinical follow-up

Bellvitge's eculizumab experience

	Yr	PreTx DSA	aAMR	Therapy	Re bx	Eculizumab	outcome
Case 1 72 yr Female 2nd KT	2010	**DSA** DR03 MFI>10000 **Negative CDC**	**11 d DSA**	rATG PF IvIg	**40 d** aAMR persistence	**600 mg** **Single dose**	**Recovery** sCr 130 No uProt
Case 2 76 yr Female 2nd KT	2012	**DSA** DR07 MFI>19000 **Negative CDC**	**3d DSA**	rATG PF IvIg	**17 d** aAMR persistence	**600 mg** **+** **600 mg after 3wks**	**Partial recovery** eGFR 26 **GS 16 m**
Case 3 40 yr Female 4th KT	2013	**No DSA** **Negative CDC**	**17d DSA** A23 MFI 4600 A24 MFI 2890 B44 MFI 2500	**Eculizumab** **900 mg** **Single dose**	**6 m** **protocol** **DSA** A23 MFI 6500 A24 MFI 4283 **scAMR** Cd4 neg	-	**Recovery** sCr 120 No uProt

Report of the Inefficacy of Eculizumab in Two Cases of Severe Antibody-Mediated Rejection of Renal Grafts

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Background. Acute antibody-mediated rejection (AMR) is responsible for up to 20% to 30% of acute rejection after kidney transplantation. New therapeutic agents have recently emerged, such as eculizumab, an anticomplement protein-C5 monoclonal antibody. In the setting of renal transplantation, eculizumab has so far proved effective both for preventive and curative treatments of AMR in sensitized patients and patients diagnosed with severe AMR. Unsuccessful eculizumab treatment has only been reported once in the literature by Stegall et al. (*Am J Transplant* 2011; 11: 2405).
Methods and Results. We present two cases of AMR resistant to eculizumab after renal transplantation. One patient received the anti-C5 antibody curatively, and the other patient developed AMR while being treated with eculizumab after a relapse of atypical hemolytic uremic syndrome. The peculiarity of these two cases was the absence of C4d deposition in peritubular capillaries as well as the absence of C1q-binding donor-specific anti–human leukocyte antigen alloantibody, as determined retrospectively, suggesting that a complement-independent mechanism underlies the pathogenesis of these AMR.
Conclusion. The use of eculizumab in C4d-negative or C1q-negative AMR does not seem effective.

Keywords: Antibody-mediated rejection, Eculizumab, Complement, Kidney transplantation.

(*Transplantation* 2014;00: 00–00)

Conclusions

- Eculizumab is useful to prevent aAMR in sensitized patients but seems to be insufficient to prevent cAMR

- Eculizumab is effective for aAMR treatment (first line and rescue therapy)