Complement Inhibition in Kidney Transplantation

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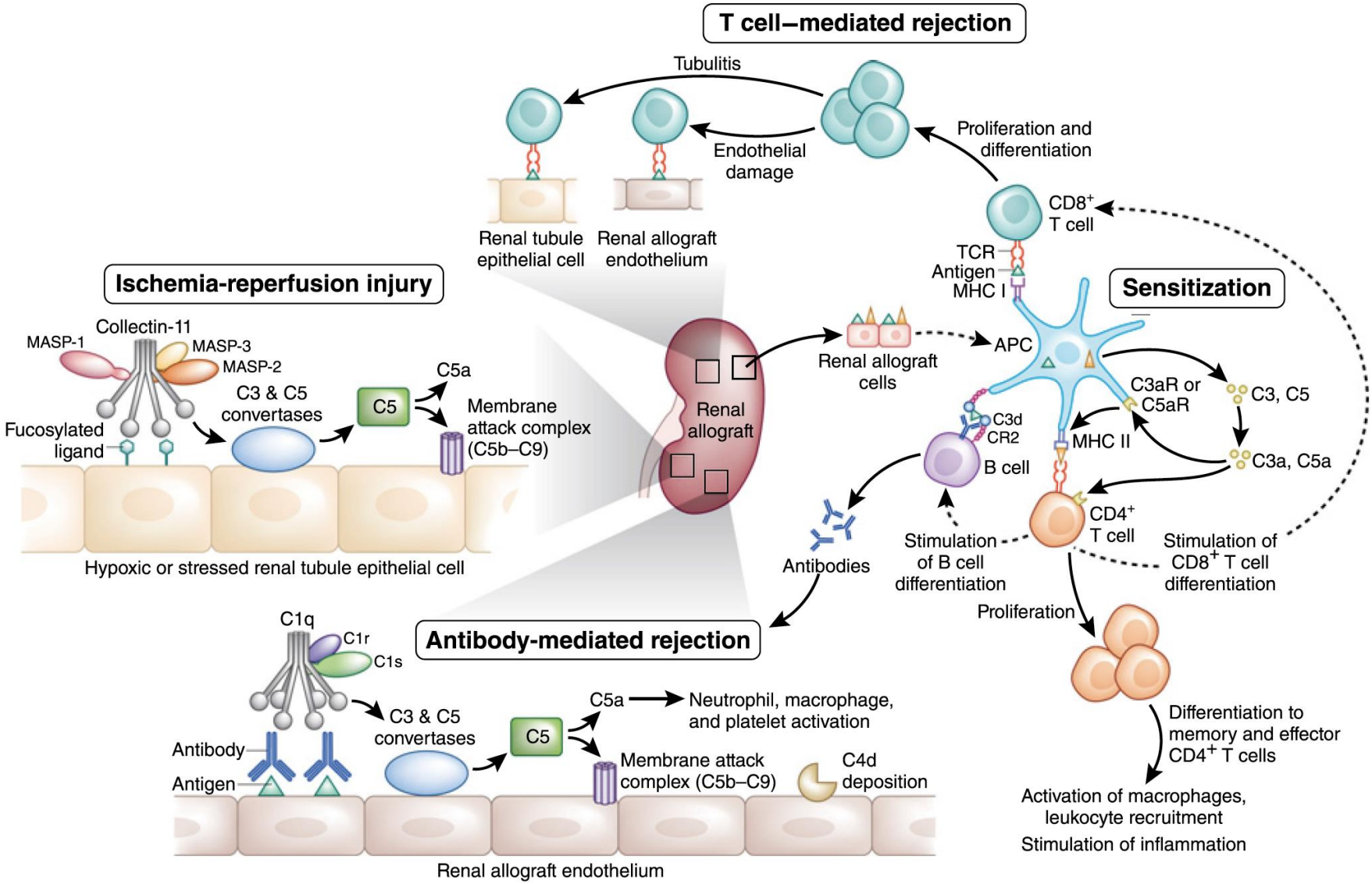
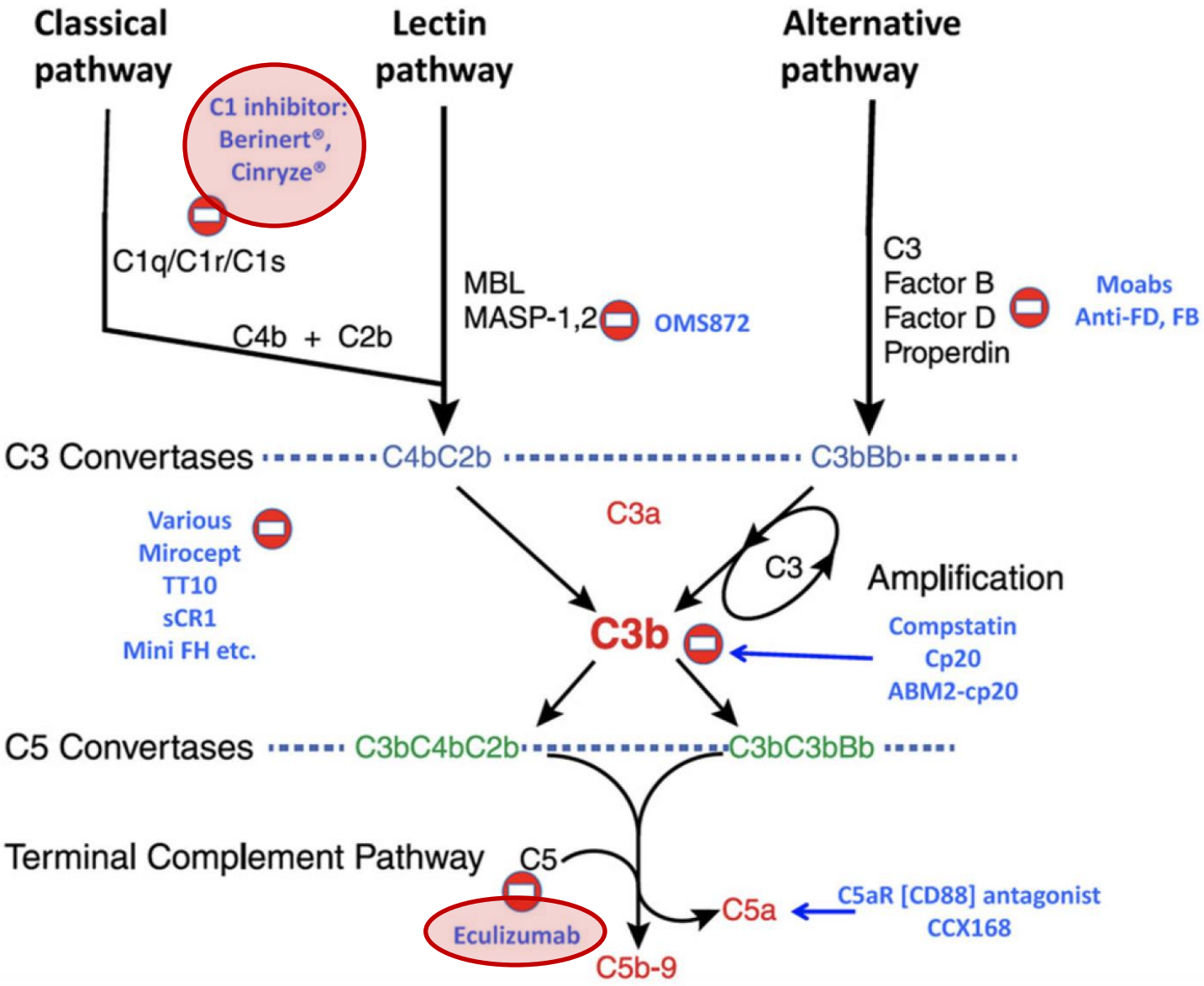
OUTLINE

- Complement inhibitors have been studied in:
  - I/R injury
  - Antibody-mediated rejection
  - Prevention of AMR in highly sensitized patients
  - Cell-mediated rejection
  - Recurrence of diseases that primarily involve the alternate pathway
  - Antiphospholipid syndrome



J Am Soc Nephrol **28:** 2571–2578, 2017



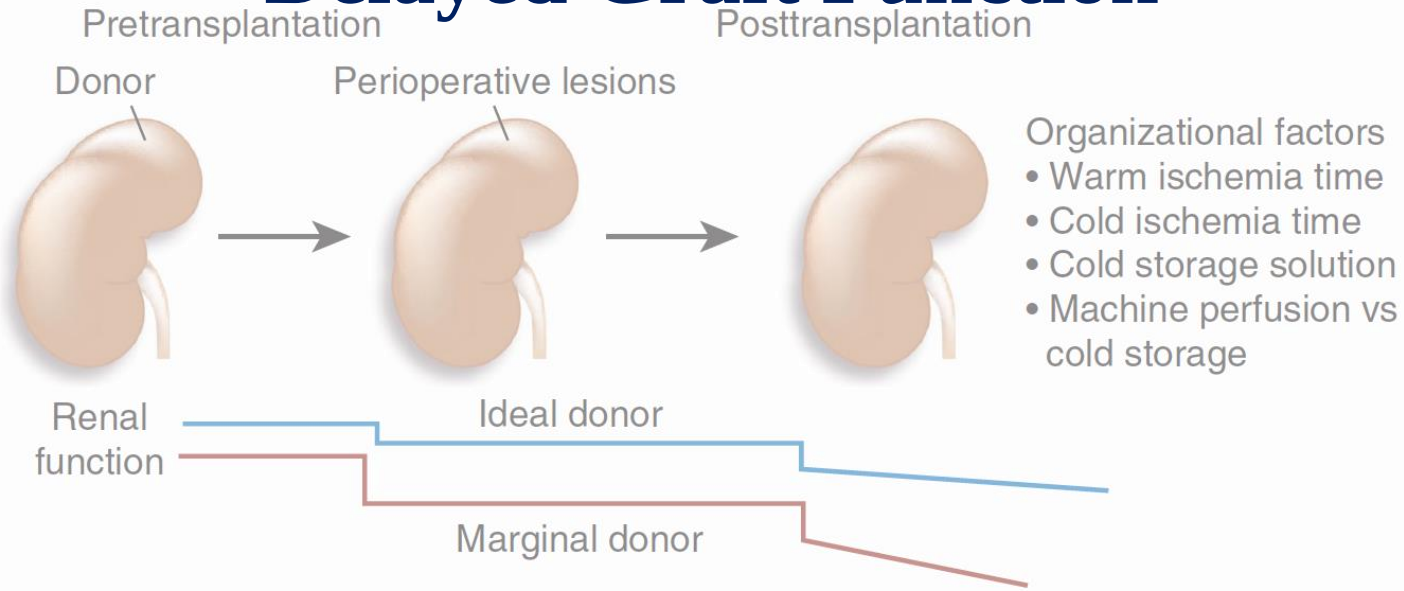
British Medical Bulletin, 2017, **124**:5–17

Delayed Graft Function

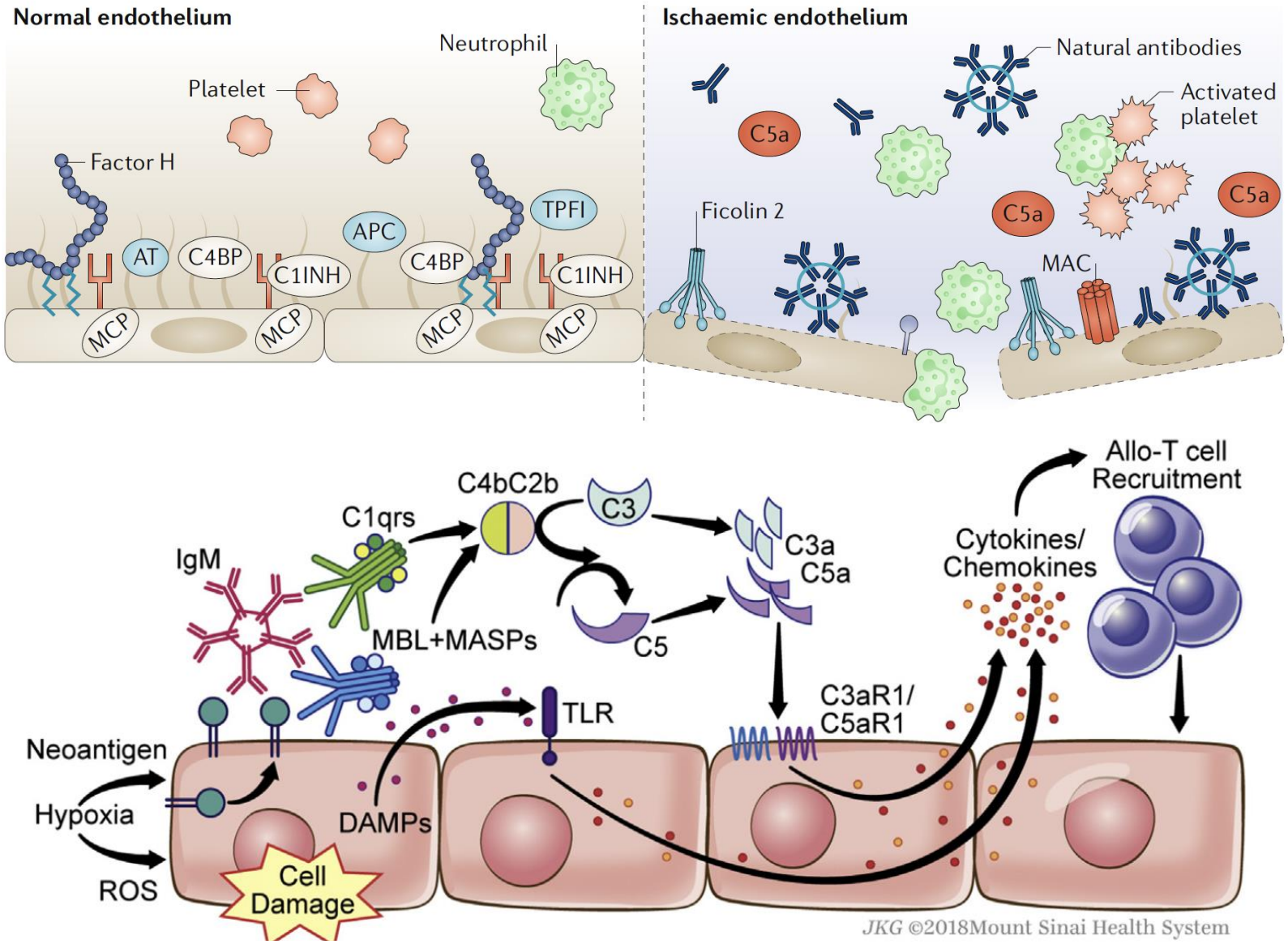
DGF diagnosis
- Urine volume
- Renal function
- Renal biopsy
- Functional imaging
- Biomarkers

Donor factors
- Age
- Living vs deceased
- SCD/ECD/DCD

Recipient factors
- Male gender
- BMI > 30
- AA background
- Dialysis requirement
- Diabetes
- HLA immunization



Organizational factors
- Warm ischemia time
- Cold ischemia time
- Cold storage solution
- Machine perfusion vs cold storage

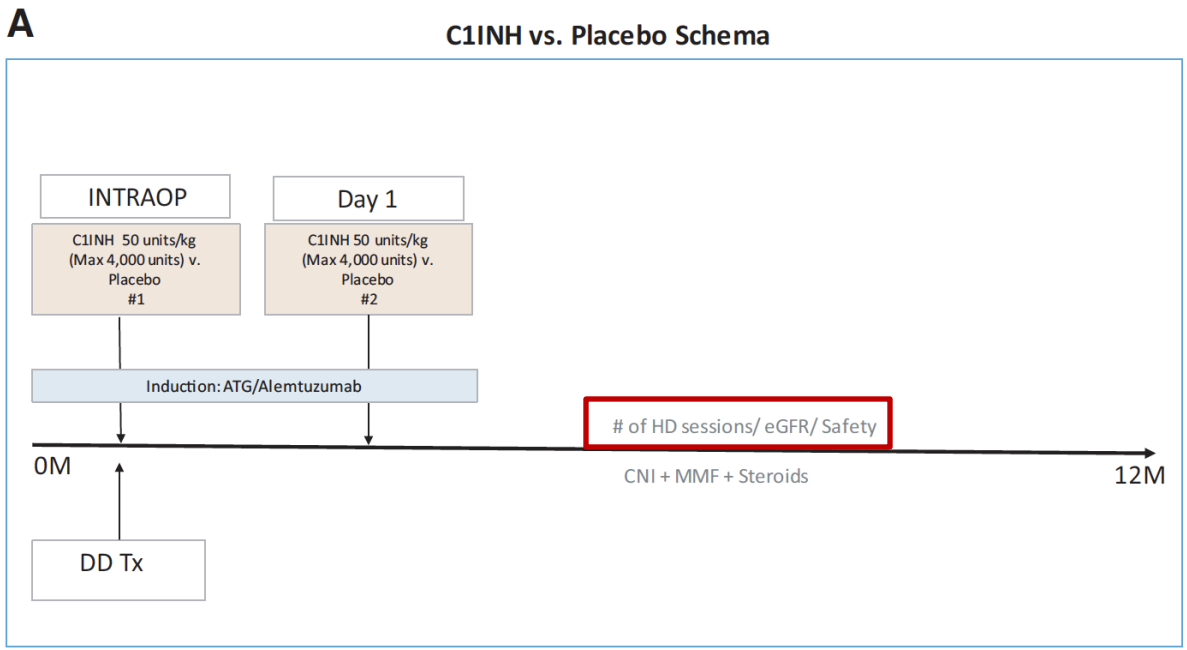


https://doi.org/10.1038/s41581-018-0071-x

Clin Lab Med ■ (2018) ■–■
https://doi.org/10.1016/j.cll.2018.10.004

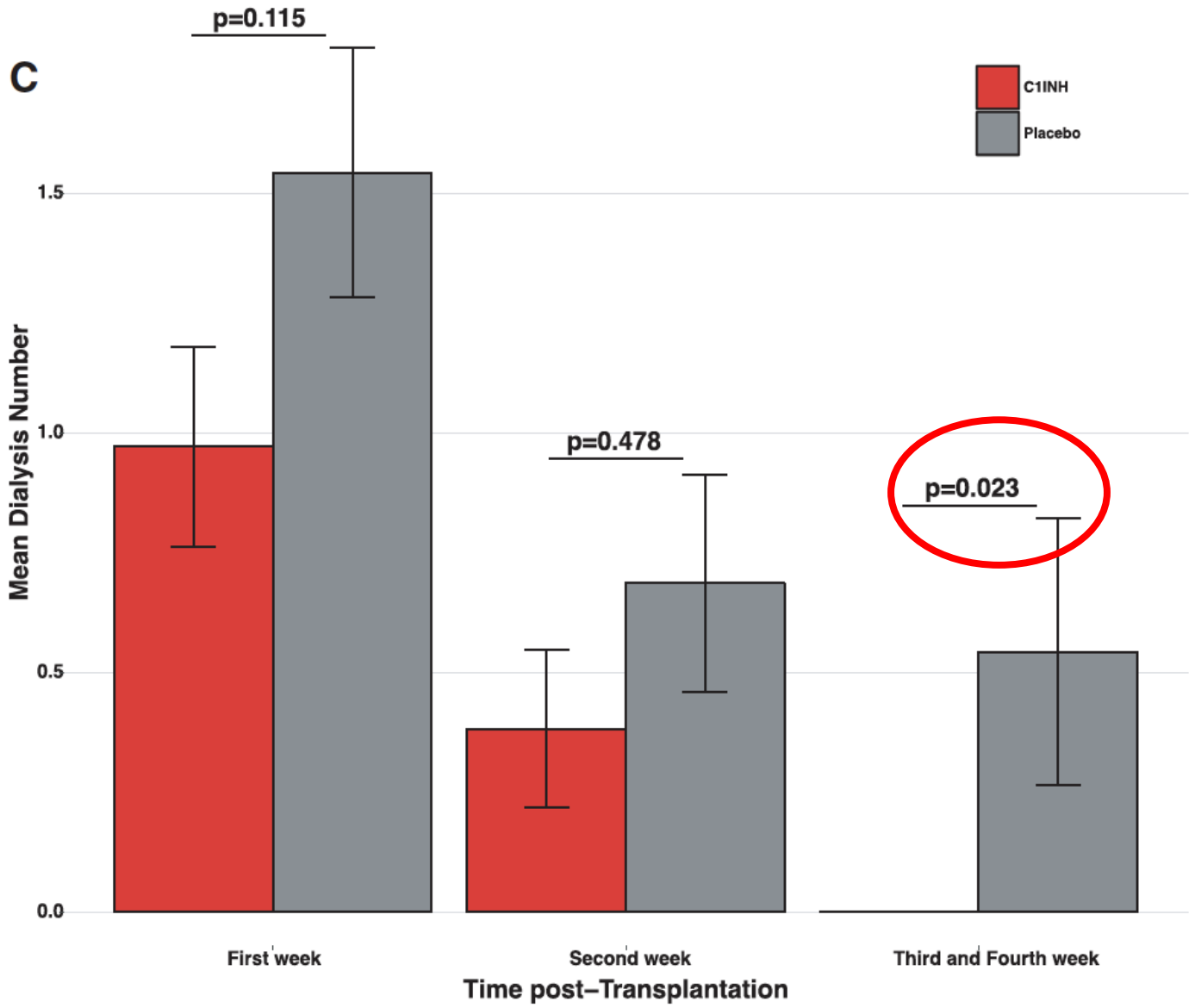
A phase I/II, double-blind, placebo-controlled study assessing safety and efficacy of C1 esterase inhibitor for prevention of delayed graft function in deceased donor kidney transplant recipients

- Recipients of kidney allografts from:
  - ECD (or KDPI score ≥85) donors,
  - DCD donors
  - DCD who have risk index of 3 to 8 (minimum 3 and maximum 8) for DGF

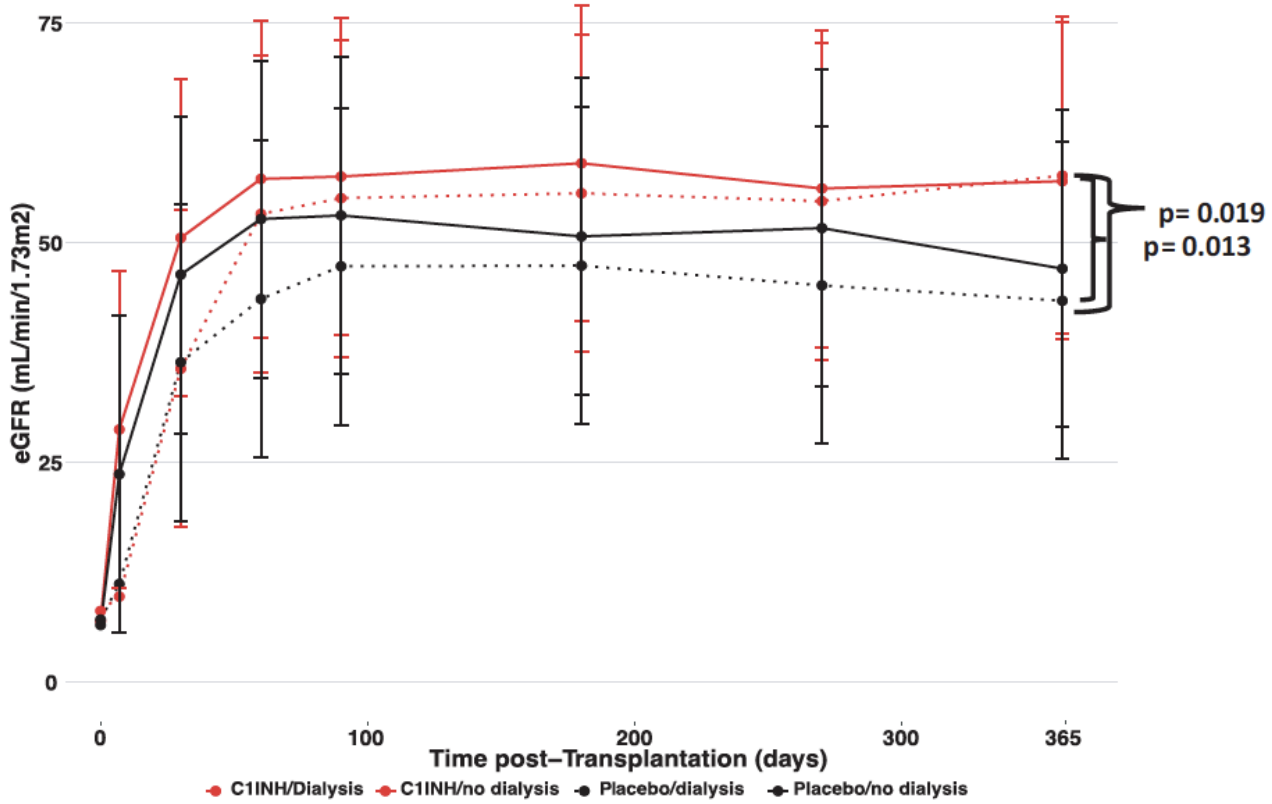


35 patients in each arm

Am J Transplant. 2018;18:2955–2964.



Am J Transplant. 2018;18:2955–2964.



Patients at highest risk for DGF (Kidney Donor Profile Index ≥85) benefited most from C1INH therapy.

Am J Transplant. 2018;18:2955–2964.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

RUCONEST® as a Therapeutic Strategy to Reduce the Incidence of Delayed Graft Function

ClinicalTrials.gov Identifier: NCT03791476

Recruitment Status : Recruiting
First Posted : January 1, 2019
Last Update Posted : June 25, 2019

See **Contacts and Locations**

CINRYZE as a Donor Pre-treatment Strategy in Kidney Recipients of KDPI>60%

ClinicalTrials.gov Identifier: NCT02435732

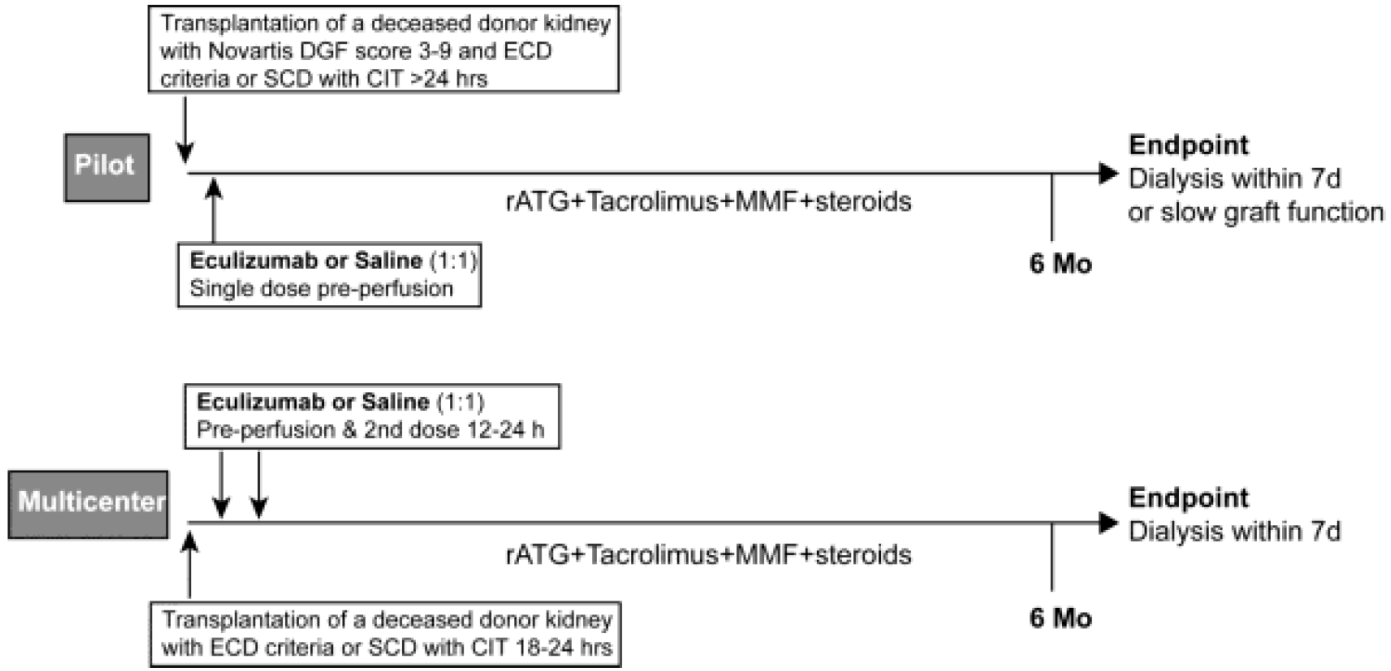
Recruitment Status : Not yet recruiting
First Posted : May 6, 2015
Last Update Posted : October 30, 2019

See **Contacts and Locations**

American Journal of Transplantation
AST AMERICAN SOCIETY OF TRANSPLANTATION ASTS

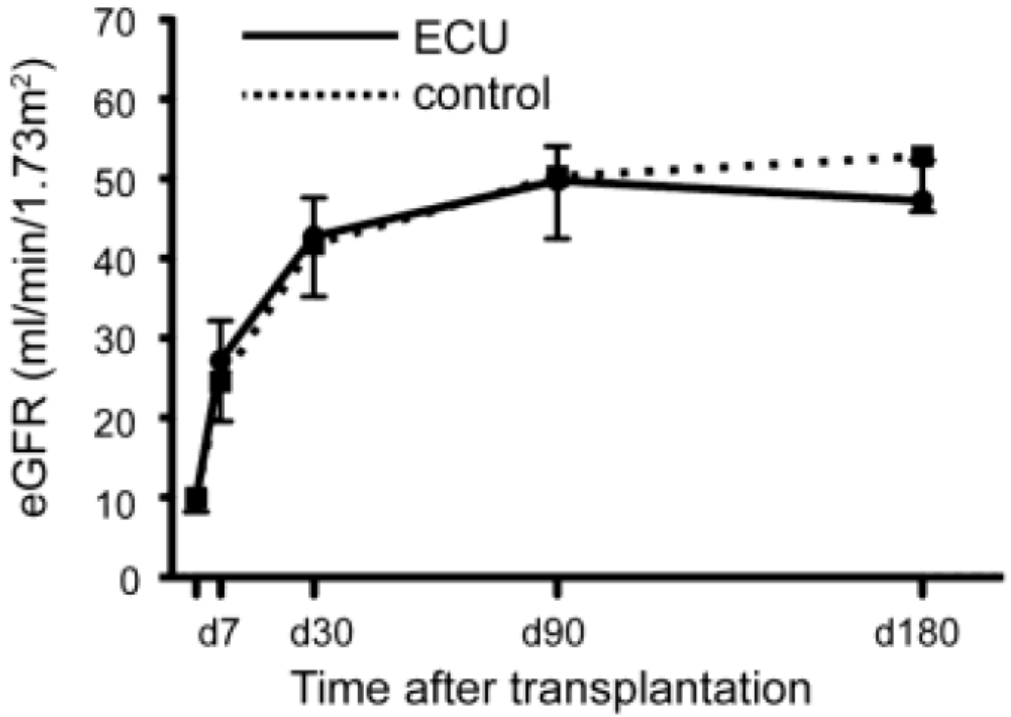
BRIEF COMMUNICATION

Peritransplant eculizumab does not prevent delayed graft function in deceased donor kidney transplant recipients: Results of two randomized controlled pilot trials



First published: 26 August 2019 | https://doi.org/10.1111/ajt.15580

	Pilot Study (N = 8)		Multicenter Study (N = 19)		Total (N = 27)		
						Con (n=11)	P*
DGF n. (%)						5 (45%)	1.0
Median days requiring dialysis						6 (1-180)	0.97
Creatinine Reduction Day 0 to Day 7 (%)						55.2 ±33.3	0.96
Creatinine Day 7 (mg/dl)						4.2 ±3.3	0.42
Graft loss, n.	0	1	0	0	0	1	



First published: 26 August 2019 | https://doi.org/10.1111/ajt.15580

Prevention of Delayed Graft Function Using Eculizumab Therapy (PROTECT Study)

Eculizumab	Placebo
Participants received 2 doses of eculizumab: the first dose was just prior to reperfusion of the allograft and the second dose was within 18 to 24 hours (h) of completion of administration of the first dose. Each dose of eculizumab was administered by intravenous (IV) infusion over 25 to 45 minutes (min). The first dose was 1200 milligrams (mg) in 240 milliliters (mL) (5 mg/mL); the second dose was 900 mg in 180 mL (5 mg/mL).	Participants received 2 doses of placebo (0.9% sodium chloride [NaCl]): the first dose was just prior to reperfusion of the allograft and the second dose was within 18 to 24 h of completion of administration of the first dose. Each dose of placebo was administered by IV infusion over 25 to 45 min. The first dose was 240 mL of 0.9% NaCl; the second dose was 180 mL of 0.9% NaCl.

ClinicalTrials.gov Identifier: NCT02145182 (Accessed November 6,2019)

	Eculizumab	Placebo
Number of participants	142	144
DGF composite	35.9	41.7
DGF	33.8	39.6
Death	0.0	1.4
Graft loss	0.7	3.5
Graft survival at 6 months	94.89	90.96
Graft survival at 12 months	92.66	88.69
Serious Adverse events	92/142 (64.79%)	102/146 (69.86%)

The incidence of DGF, death, graft loss, or loss to follow-up at 7 days posttransplant was 35.9% on treatment, compared to 41.7% for patients receiving placebo ($p = 0.398$). Nephron 2019;143:193–196

ClinicalTrials.gov Identifier: NCT02145182 (Accessed November 6,2019)

NIH U.S. National Library of Medicine

ClinicalTrials.gov

A Study of the Activity of Eculizumab for Prevention of Delayed Graft Function In Deceased Donor Kidney Transplant

ClinicalTrials.gov Identifier: NCT01403389

Recruitment Status : Terminated (After interim analysis, the pilot study was terminated and modified to a larger multicenter study (NCT01919346) to better assess efficacy.)
First Posted : July 27, 2011
Last Update Posted : May 6, 2019

Eculizumab for Prevention of Delayed Graft Function (DGF) in Kidney Transplantation

ClinicalTrials.gov Identifier: NCT01919346

Recruitment Status : Terminated (Based on results from Alexion PROTECT DGF study)
First Posted : August 9, 2013
Last Update Posted : February 27, 2018

- Based on these results, it seems that prevention of DGF requires proximal complement inhibition (at or prior to the C3 convertase step).

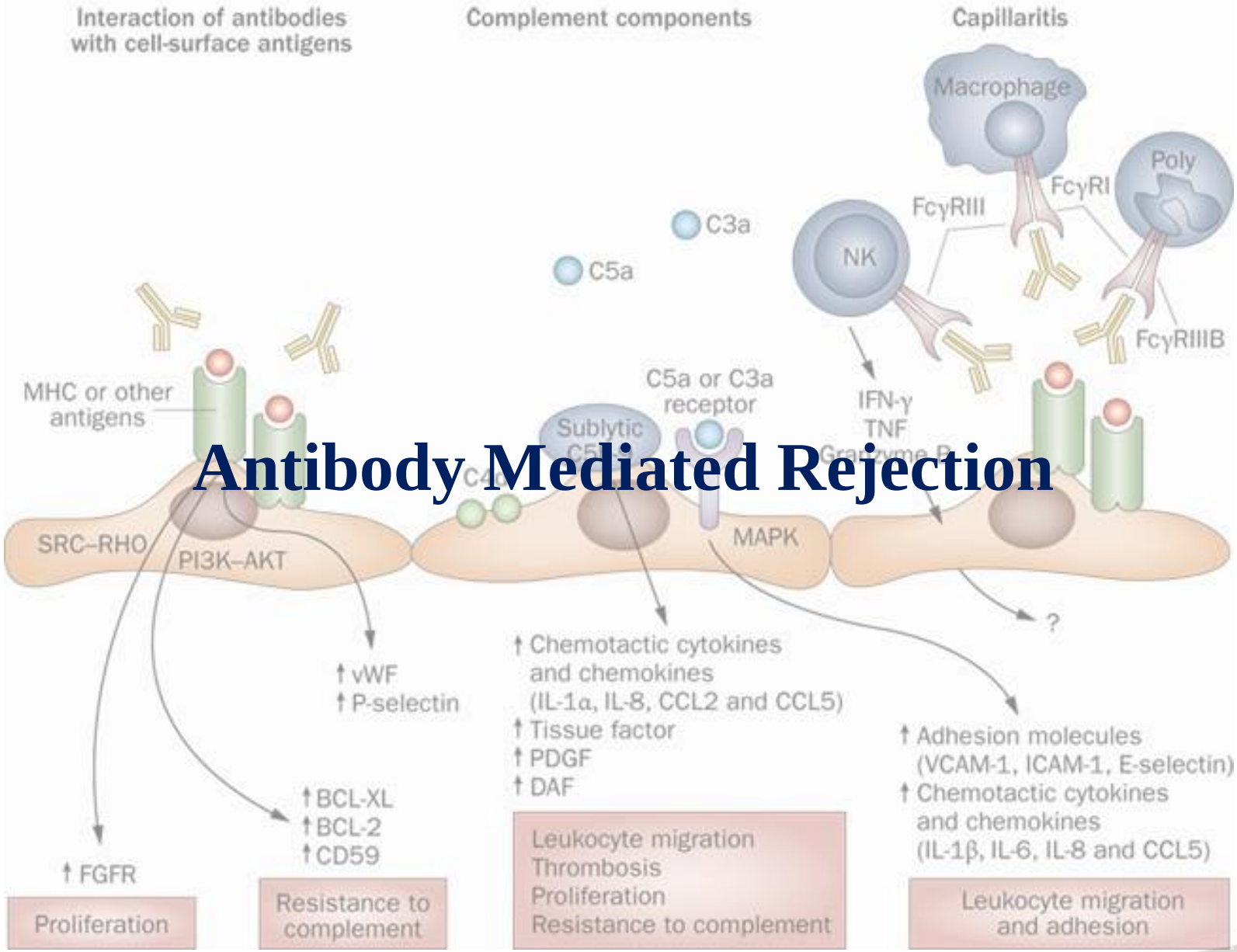
Drug	Description of the drug	Mechanism of action	Phase of clinical development
sCR1, TT10	Soluble form of recombinant CR1	Inactivation of C3b	Inconclusive results in cardiac surgery and in dense deposit disease
APT070, Mirococept	Truncated CR1 with lipopeptide membrane	Inactivation of C3b	Clinical trial for preventing ischemia-reperfusion injury in the kidney allograft
TT30 (Alexion)	Fusion protein between CCP1-4 FH and CCP1-4 CR2	Inactivation of C3b	Preclinical

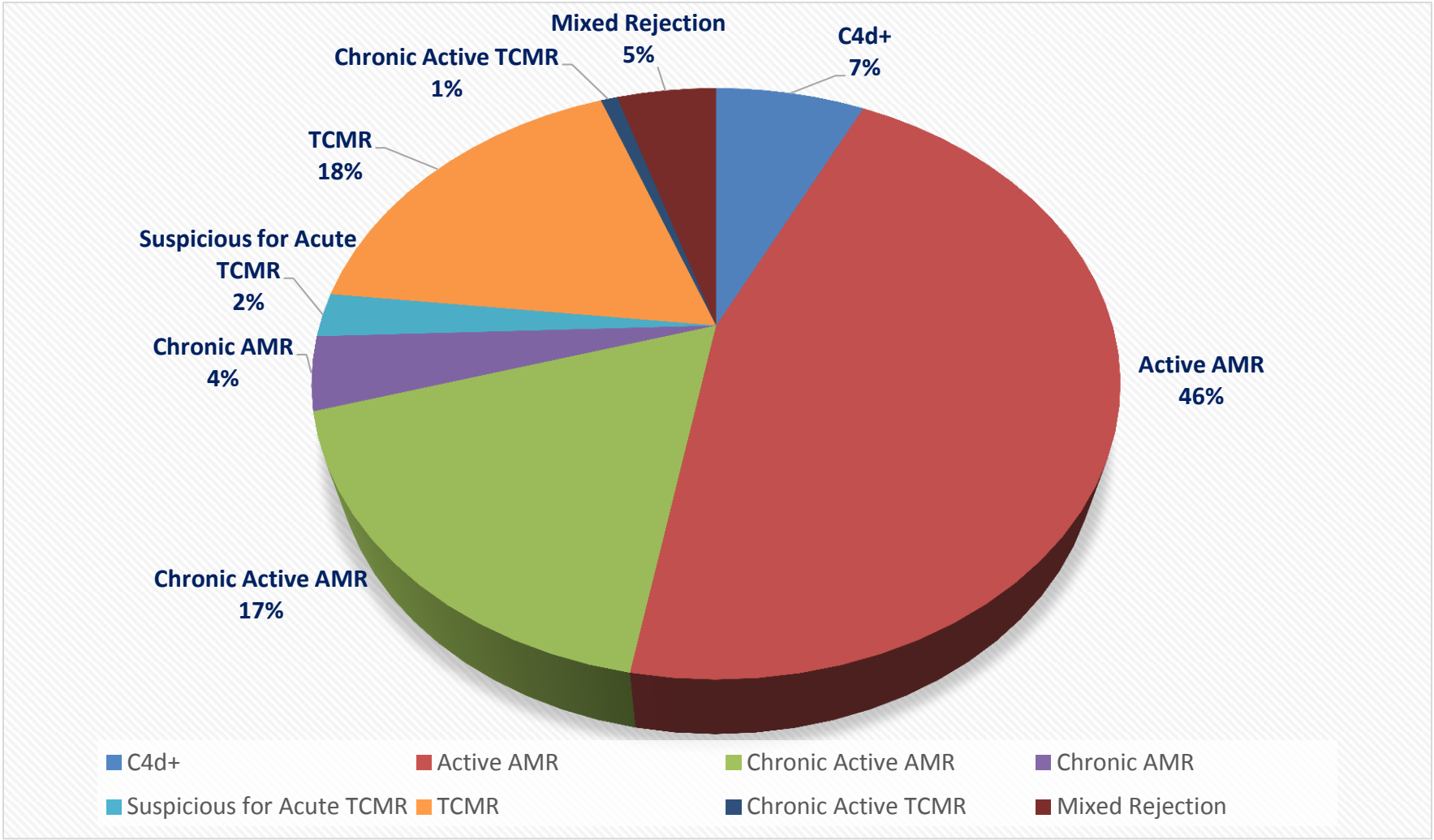
A double-blind randomised controlled investigation into the efficacy of Mirococept (APT070) for preventing ischaemia reperfusion injury in the kidney allograft (EMPIRIKAL): study protocol for a randomised controlled trial

Recruitment is completed

No result posted yet

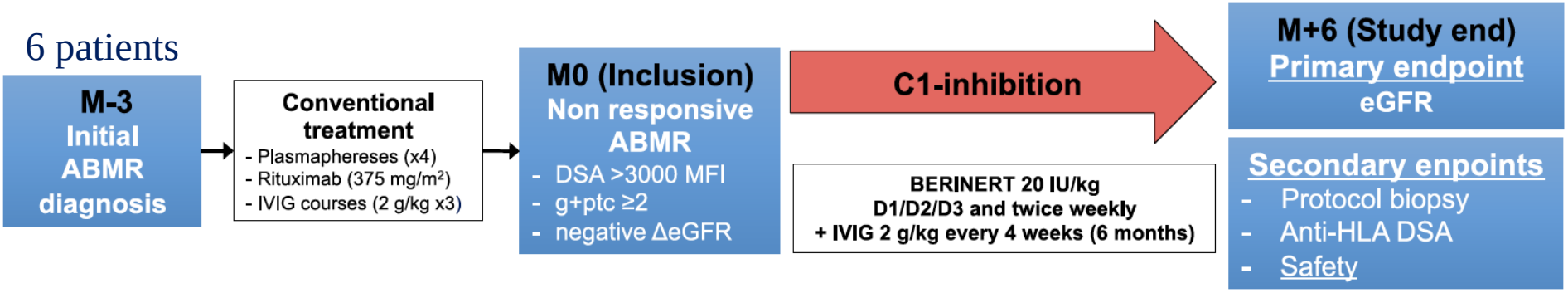
Antibody Mediated Rejection





Unpublished personal data

C1 Inhibitor in Acute Antibody-Mediated Rejection Nonresponsive to Conventional Therapy in Kidney Transplant Recipients: A Pilot Study



American Journal of Transplantation 2016; 16: 1596–1603

Table 3: Immunological, clinical, and histological changes between M0 and M+6 in C1-INH patients

	M0 n = 6	M+6 n = 6	p-value
Characteristics of anti-HLA DSA			
Number, mean ± SD	2.0 ± 0.6	2.0 ± 0.6	–
HLA class specificity, n (%)			–
HLA class I	2 (33.3)	2 (33.3)	
HLA class II	3 (50.0)	3 (50.0)	
HLA class I + II	1 (16.7)	1 (16.7)	
MFI sum, mean±SE	17 469.0 ± 3833.7	14 872.2 ± 3307.9	0.0277
MFI mean, mean±SE	9806.4 ± 2472.6	10 395.5 ± 3071.1	0.9165
Clinical characteristics			
eGFR (mL/min/1.73 m^2), mean ± SD	38.7 ± 17.9	45.2 ± 21.3	0.0277
Proteinuria (g/g), mean ± SD	0.5 ± 0.4	0.7 ± 0.6	0.2059
Histological characteristics (Banff scores)			
g + ptc score, mean ± SD	3.7 ± 1.0	3.0 ± 1.1	0.1585
i + t score, mean ± SD	0.3 ± 0.8	0	0.3173
v score, mean ± SD	0.2 ± 0.4	0	0.3173
cg score, mean ± SD	0.3 ± 0.5	0.5 ± 0.5	0.3173
IF/TA score, ean ± SD	1.2 ± 0.4	1.7 ± 1.0	0.4235
cv score, mean ± SD	1.2 ± 0.4	1.5 ± 0.5	0.1573
C4d deposition, n (%)	5 (83.3)	1 (16.7)	0.0455

American Journal of Transplantation 2016; 16: 1596–1603

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

Placebo	CINRYZE
Participants received an intravenous (IV) infusion of normal saline, at a rate of approximately 1 mL per minute as tolerated, 7 times over a 2-week period: an initial infusion on Day 1, followed by infusions on Days 3, 5, 7, 9, 11, and 13.	Participants received an intravenous (IV) infusion of human C1 esterase inhibitor (CINRYZE) at a rate of approximately 1 mL per minute as tolerated. Participants received a total of 7 doses over a 2-week period: an initial IV infusion of 5000 U (not to exceed 100 U/kg) on Day 1, followed by 2500 U (not to exceed 50 U/kg) IV on Days 3, 5, 7, 9, 11, and 13.

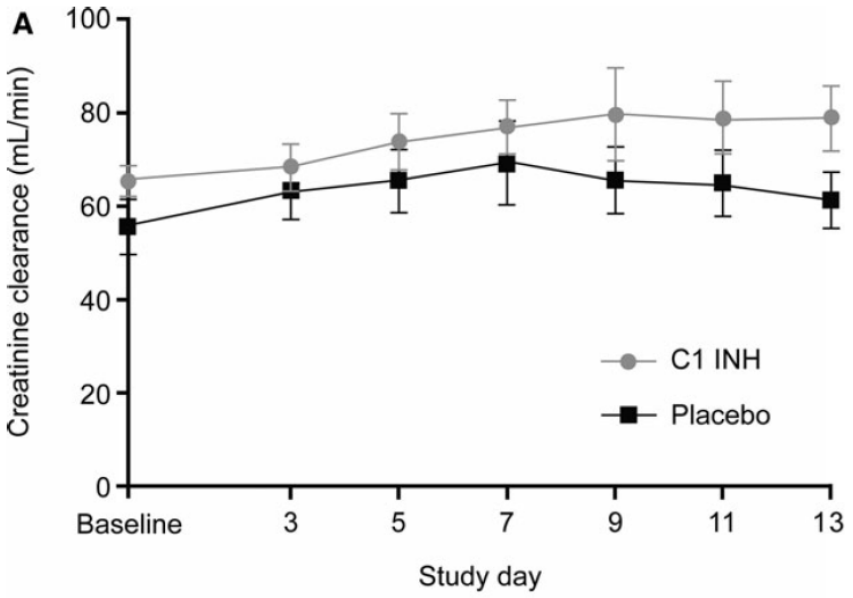
A 2-week course of C1- INH (Cinryze, Shire Pharmaceuticals) as an add-on therapy to SOC plasmapheresis and low-dose IVIg, compared to SOC alone.

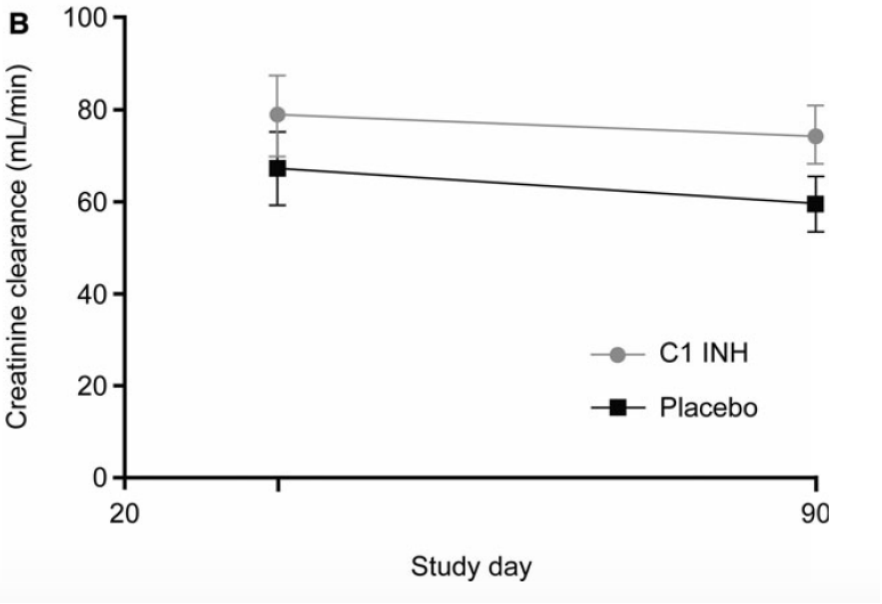
American Journal of Transplantation 2016; 16: 3468–3478

Table 4: Change in histopathology scores from qualifying biopsy to day-20 biopsy

Histopathology end point	Placebo (n = 9)			C1 INH (n = 9)			p-value for treatment difference[1]
	Qualifying biopsy	Day-20 biopsy	Change	Qualifying biopsy	Day-20 biopsy	Change	
C4d score							
Mean ± SD	60.8 ± 41.2	15.8 ± 32.9	−45.0 ± 46.9	68.7 ± 41.8	32.6 ± 39.1	−36.1 ± 33.4	0.6498
Margination score							
Mean ± SD	23.0 ± 24.8	17.0 ± 25.8	−6.0 ± 14.0	9.2 ± 15.2	21.8 ± 29.3	12.6 ± 25.9	0.0768
Glomerulitis score							
Mean ± SD	17.0 ± 24.9	23.7 ± 30.9	6.7 ± 26.6	16.3 ± 23.4	19.0 ± 28.8	2.7 ± 13.6	0.6928
Vasculitis score							
Mean ± SD	3.9 ± 7.8	0 ± 0.0	−3.9 ± 7.8	0 ± 0.0	3.2 ± 6.4	3.2 ± 6.4	0.0508
Glomerulosclerosis score							
Mean ± SD	4.2 ± 6.8	2.8 ± 3.6	−1.4 ± 7.8	8.9 ± 9.6	2.6 ± 4.3	−6.3 ± 7.9	0.2042
Chronic glomerulopathy score							
Mean ± SD	0.3 ± 1.0	0.6 ± 1.7	0.2 ± 0.7	0 ± 0.0	0 ± 0.0	0 ± 0.0	0.3322
Interstitial fibrosis score							
Mean ± SD	3.2 ± 6.6	9.1 ± 14.1	5.9 ± 9.8	0.7 ± 1.3	12.2 ± 20.4	11.6 ± 20.9	0.4723
Chronic vasculitis score							
Mean ± SD	8.3 ± 12.8	6.7 ± 11.7	−1.7 ± 18.2	2.6 ± 4.5	5.4 ± 7.7	2.9 ± 9.0	0.5103

American Journal of Transplantation 2016; 16: 3468–3478

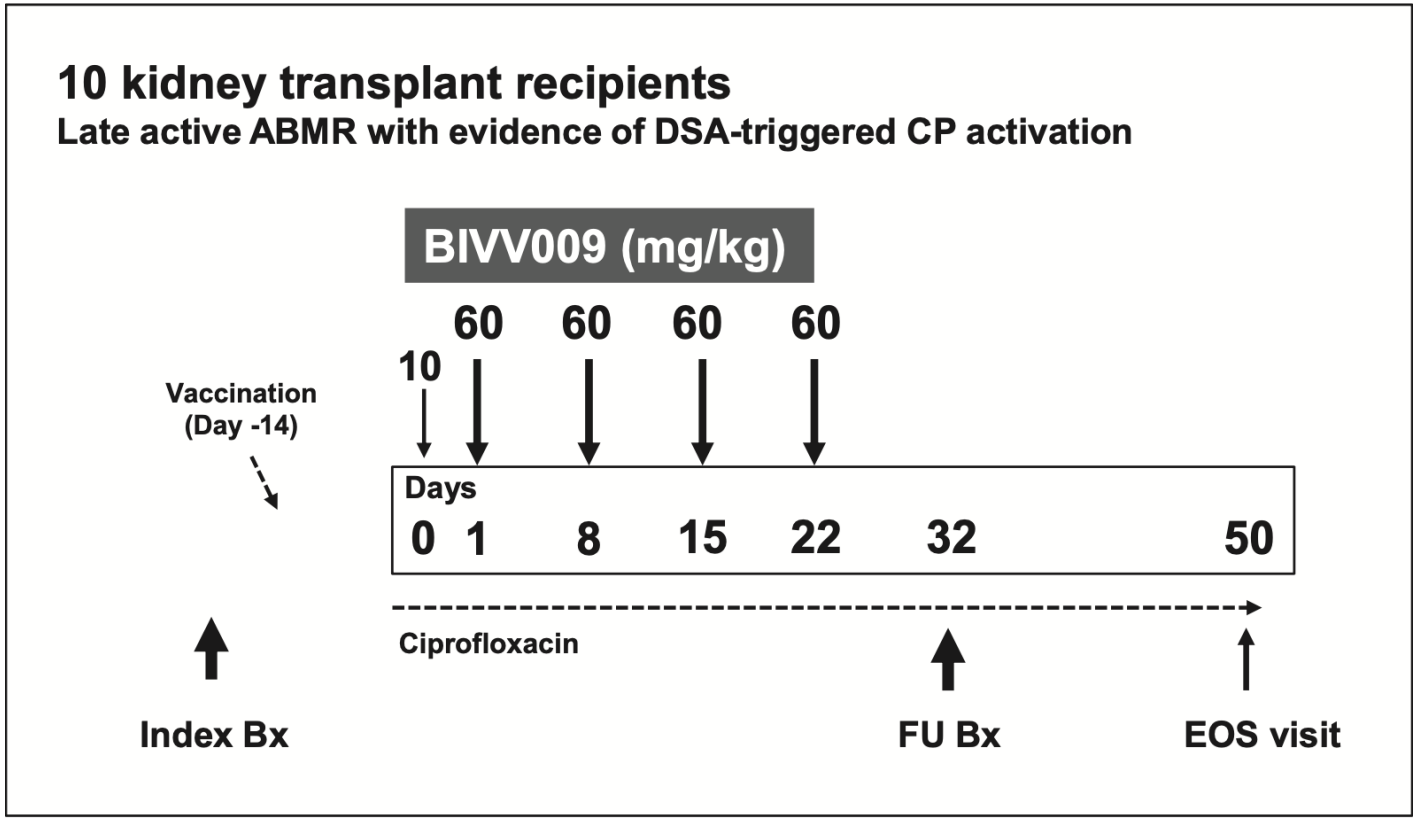




- C1 INH group demonstrated a trend toward sustained improvement in renal function.
- Six-month biopsies performed in 14 subjects (C1 INH = 7, placebo = 7) showed no transplant glomerulopathy (TG) (PTC+cg≥1b) in the C1 INH group, whereas 3 of 7 placebo subjects had TG.

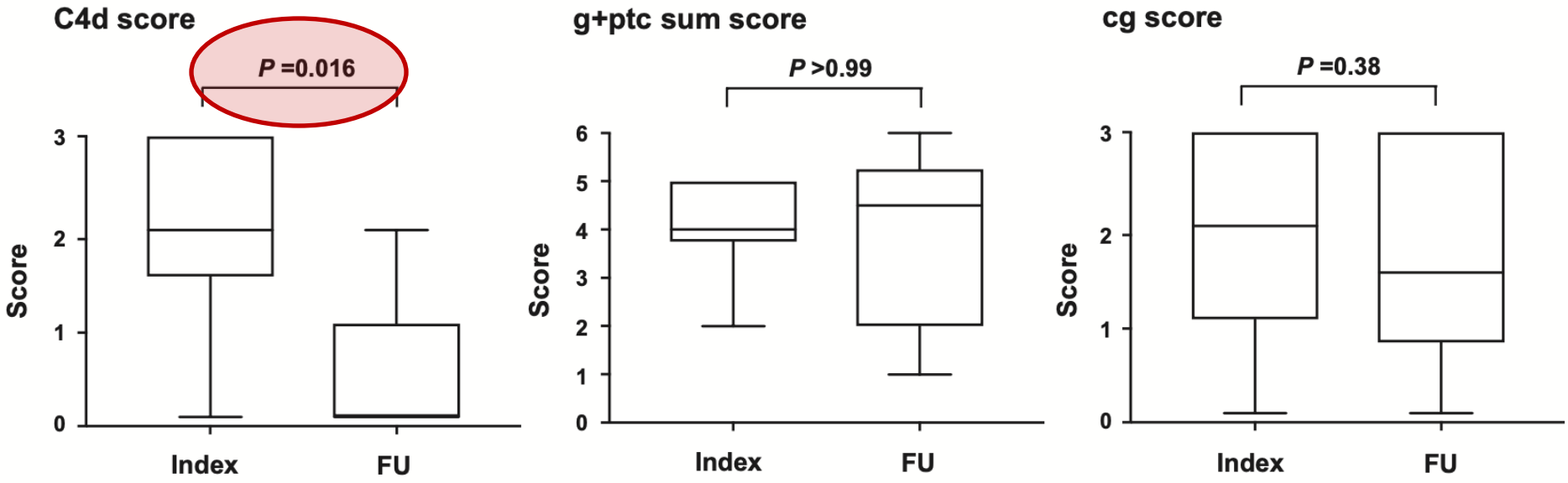
American Journal of Transplantation 2016; 16: 3468–3478

Anti-C1s monoclonal antibody BIVV009 in late antibody-mediated kidney allograft rejection—results from a first-in-patient phase 1 trial



Am J Transplant. 2018;18:916–926.

5-week follow-up biopsies



BIVV009 effectively blocks alloantibody-triggered CP activation, even though short-course treatment had no effect on indices of activity and chronicity of ABMR.

Use of Eculizumab for Active Antibody-mediated Rejection That Occurs Early Post–kidney Transplantation

A Consecutive Series of 15 Cases

Tan, Ek Khoon MBBS[1]; Bentall, Andrew MD[2,3]; Dean, Patrick G. MD[1,3]; Shaheen, Mohammed F. MBBS[1]; Stegall, Mark D. MD[1,3]; Schinstock, Carrie A. MD[2,3]

Transplantation: November 2019 - Volume 103 - Issue 11 - p 2397–2404
doi: 10.1097/TP.0000000000002639

	Trial	Status
NCT02113891	**Eculizumab Therapy for Subclinical Antibody-mediated Rejection in Kidney Transplantation (TAMARCIN)**	Withdrawn
NCT01895127	**Efficacy and Safety of Eculizumab for Treatment of Antibody-mediated Rejection Following Renal Transplantation**	Terminated due to lack of efficacy

Clinicaltrials.gov (Accessed November 6,2019)

- These findings suggest that complement inhibition upstream of C5 with C1 inhibition and blocking the generation of complement activation products of C3 might have crucial role in treatment of AMR .

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Efficacy and Safety of Human Plasma-derived C1-esterase Inhibitor as add-on to Standard of Care for the Treatment of Refractory Antibody Mediated Rejection (AMR) in Adult Renal Transplant Recipients

ClinicalTrials.gov Identifier: NCT03221842

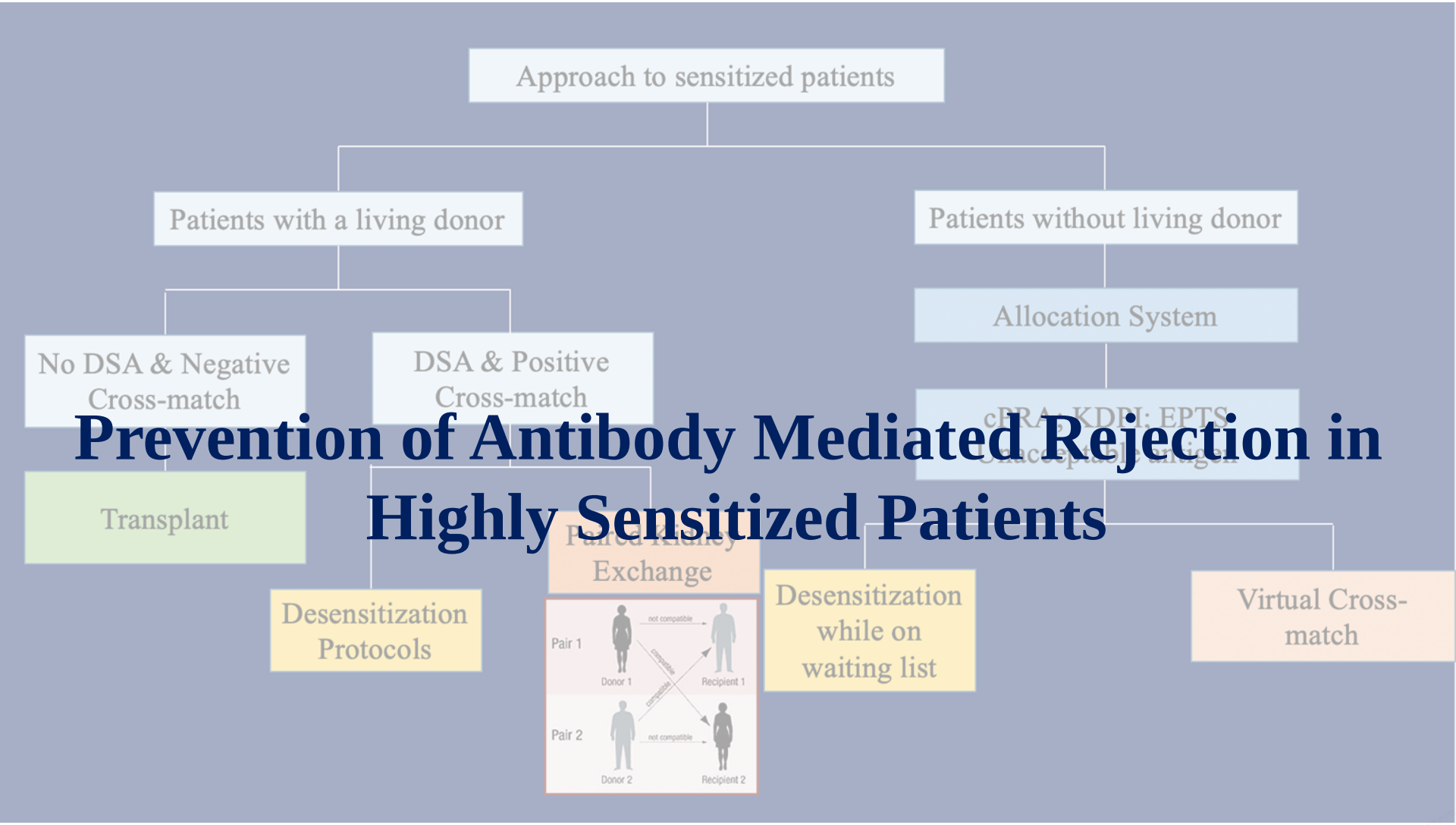
Recruitment Status : Recruiting

First Posted : July 19, 2017

Last Update Posted : October 2, 2019

See **Contacts and Locations**

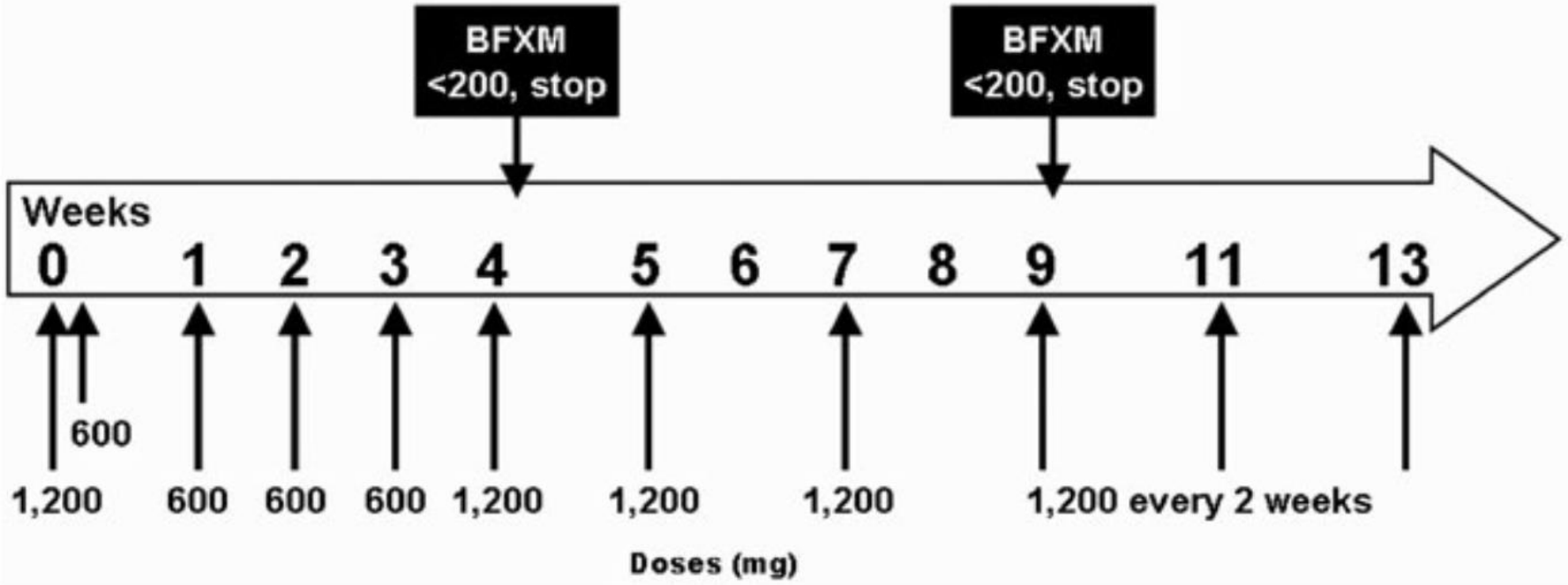
Prevention of Antibody Mediated Rejection in Highly Sensitized Patients



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

Anti-C5 Treatment Protocol

Base- line BFXM against their living donor with a channel shift <450 and ≥200.



Started in 2008

American Journal of Transplantation 2011; 11: 2405–2413

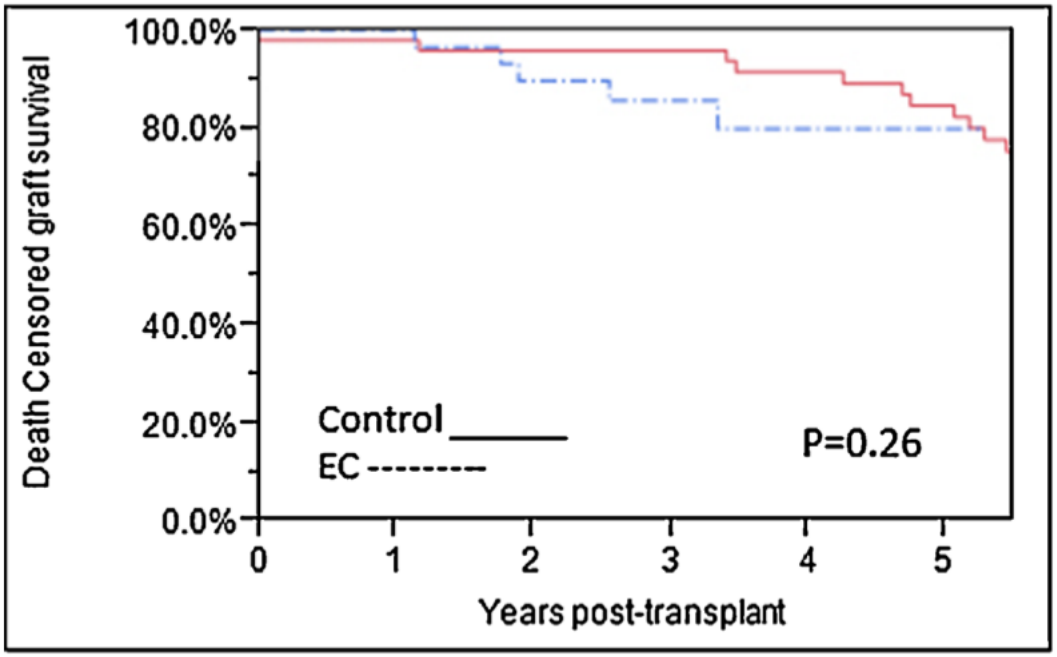
Table 2: Posttransplant outcomes in the eculizumab-treated and control groups

Category	Eculizumab group (n = 26)	Historical 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.

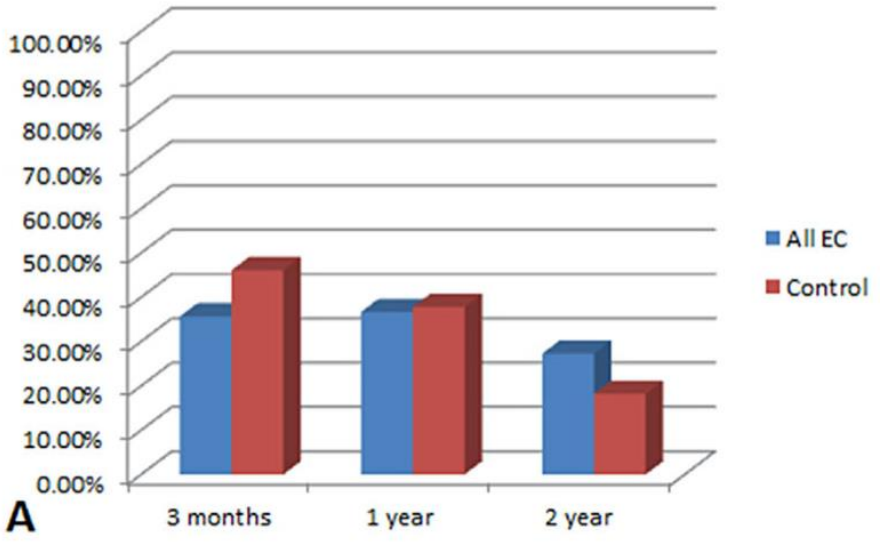
American Journal of Transplantation 2011; 11: 2405–2413

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

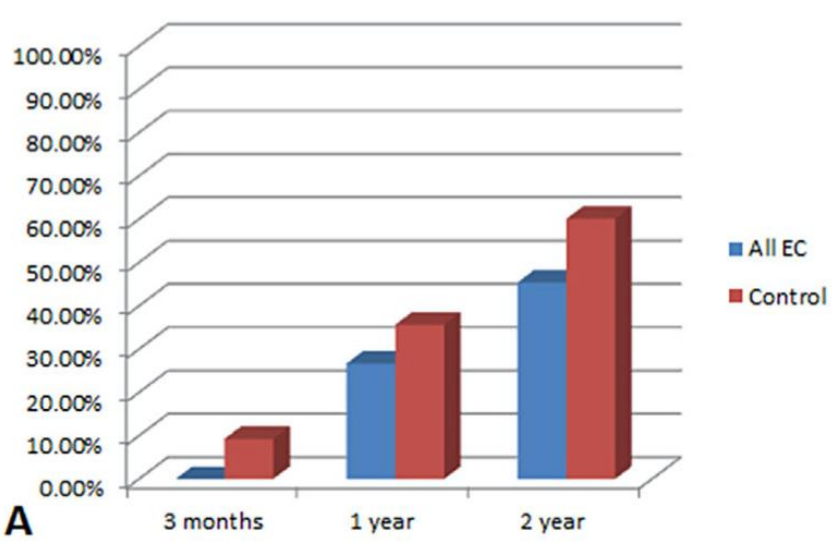


At risk	0	1	2	3	4	5
Control	48	46	46	45	40	37
EC	30	30	26	21	8	2

American Journal of Transplantation 2015; 15: 1293–1302



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

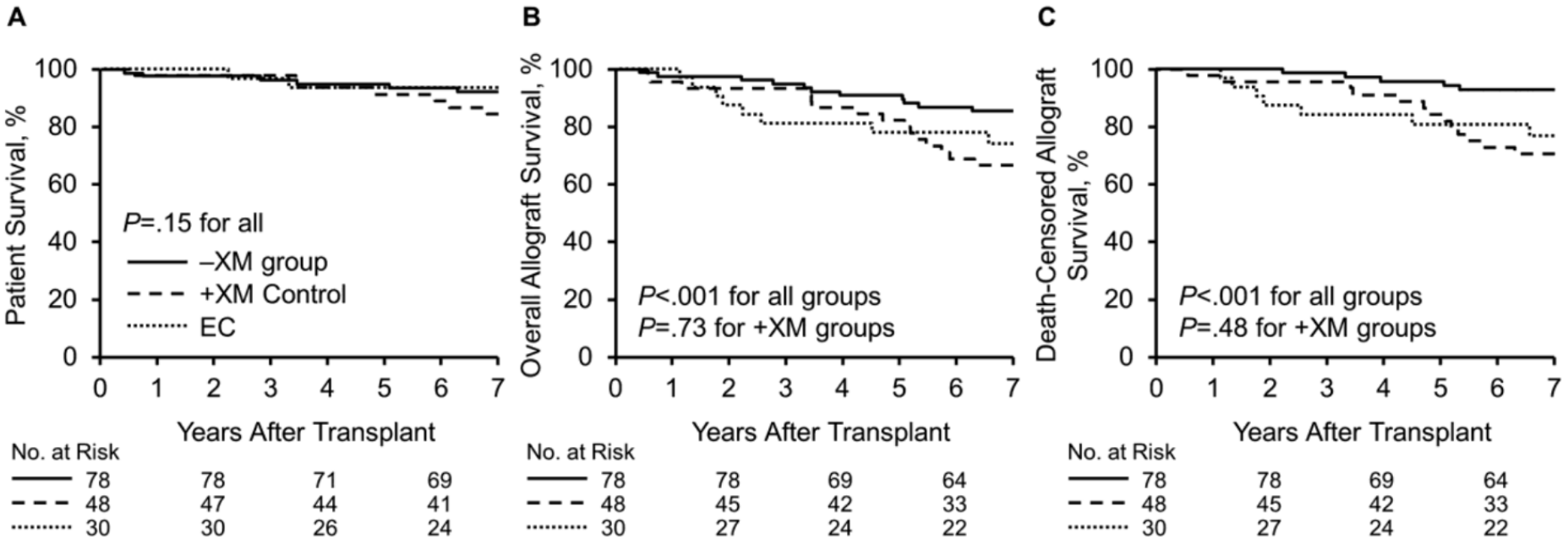


Transplant Glomerulopathy in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	0% (0/28)	26.7% (8/30)	45.4% (10/22)
Control	9.3% (4/43)	39.5% (15/38)	63.6% (21/33)
p-value (EC vs. control)	P=0.15	P=0.31	P=0.27

Despite decreasing acute clinical ABMR rates, EC treatment does not prevent chronic ABMR in recipients with persistently high BFXM after +XMKTx.

American Journal of Transplantation 2015; 15: 1293–1302

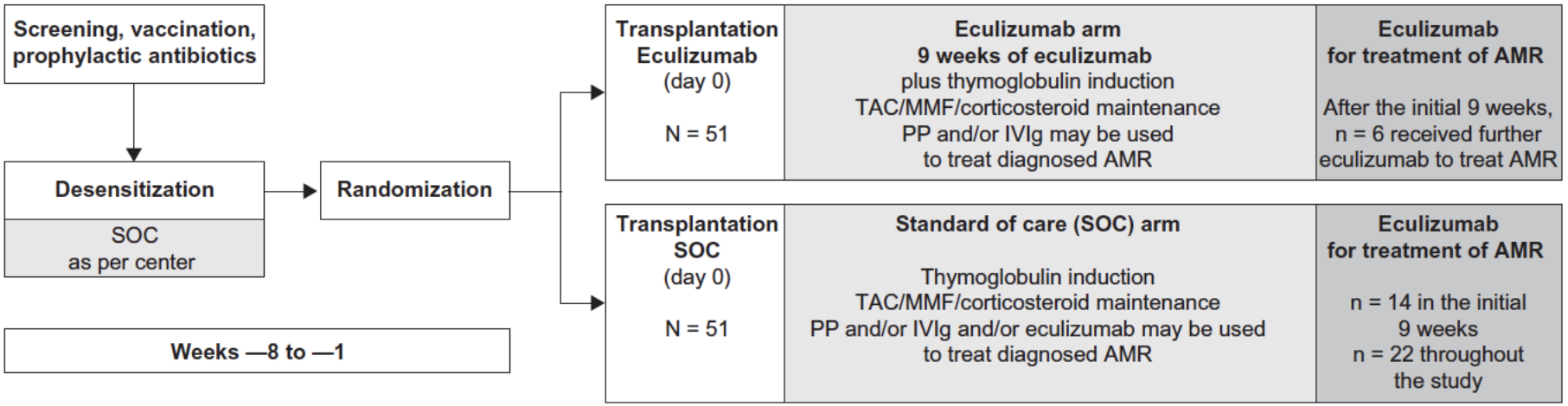
Long-term outcomes of eculizumab-treated positive crossmatch recipients: Allograft survival, histologic findings, and natural history of the donor-specific antibodies



+XM kidney transplant recipients who received eculizumab after transplant remained at high risk for CAMR and had similar long-term outcomes as historical +XM control.

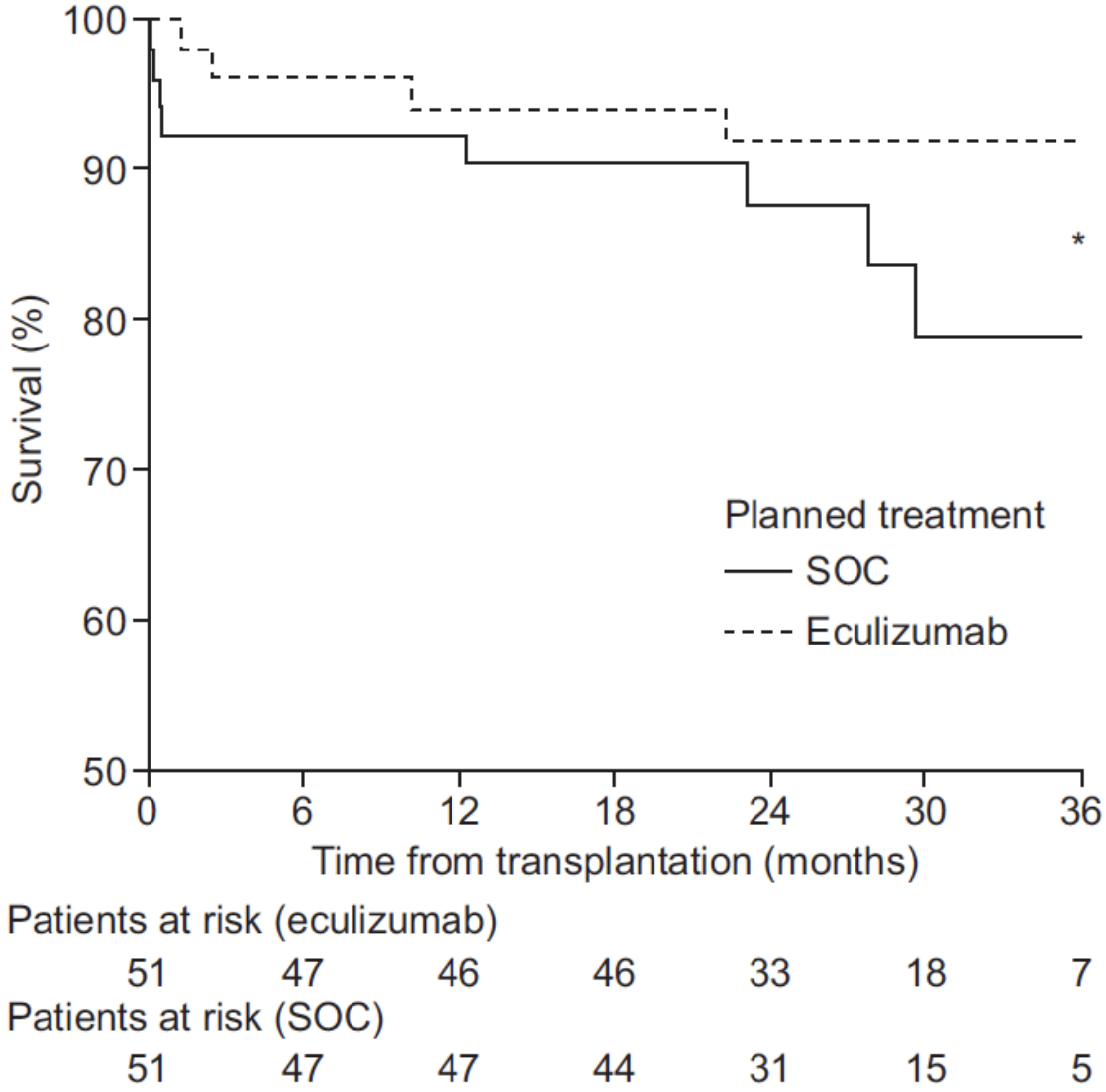
Am J Transplant. 2019 Jun;19(6):1671-1683

Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy: A randomized trial



Dosing protocol	Pretreatment		Transplantation		Induction phase				Maintenance phase				
	Neisseria meningitidis vaccination ≥14 days before transplantation	Week			1	2	3	4	5	6	7	8	9
		Day	0	1	7	14	21	28					
		Eculizumab dose, mg	1200	900	900	900	900	900	1200	0	1200	0	1200

Am J Transplant. 2019;19:2876–2888.



*P = .209

Am J Transplant. 2019;19:2876–2888.

TABLE 5 Treatment failure rate (reassessed central and local pathology, with and without grade I antibody-mediated rejection included)

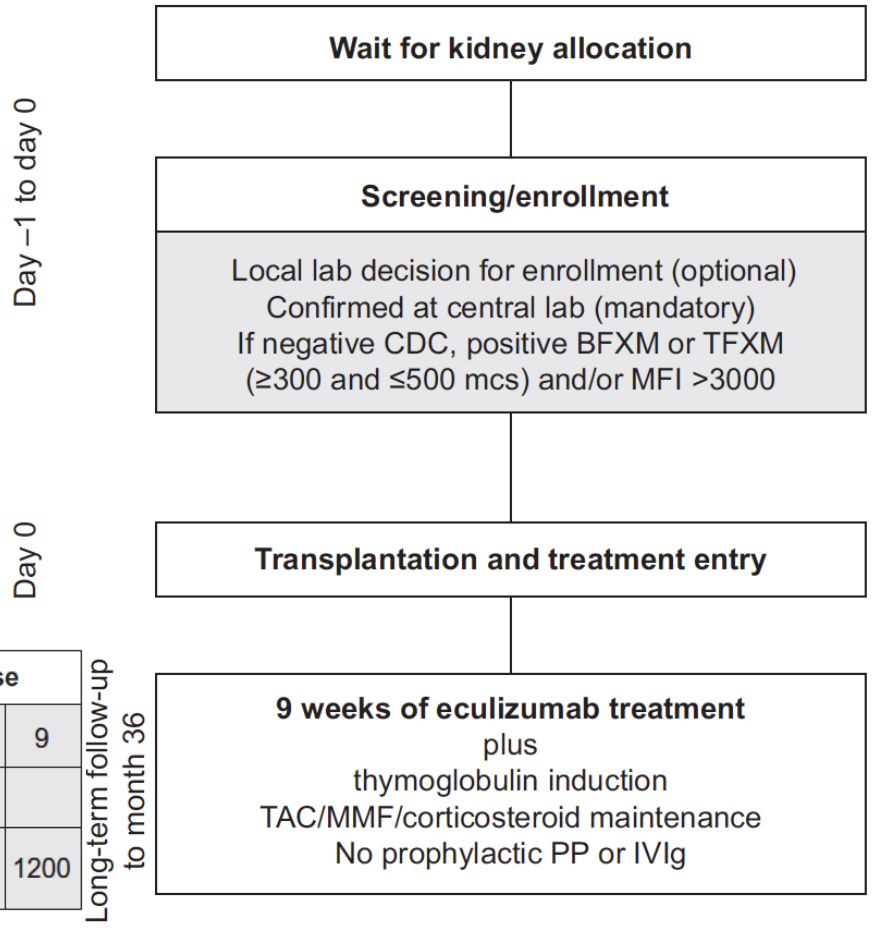
AMR	Location	End point	Eculizumab (N = 51) n (%)	SOC (N = 51) n (%)	Difference (exact 95% CI)	*P* value
Grade II or III acute AMR only	Central[a,b]	Treatment failure	6 (11.8)	11 (21.6)	−9.8% (−29.6, 10.5)	.288
		AMR	6 (11.8)	9 (17.6)		
		Graft loss	1 (2.0)	4 (7.8)		
		Death	1 (2.0)	1 (2.0)		
		Loss to follow-up	0 (0.0)	0 (0.0)		

This finding suggests a potential benefit for eculizumab compared with SOC in preventing acute AMR in recipients sensitized to their living-donor kidney transplants.

Am J Transplant. 2019;19:2876–2888.

Safety and efficacy of eculizumab for the prevention of antibody-mediated rejection after deceased-donor kidney transplantation in patients with preformed donor-specific antibodies

Study design

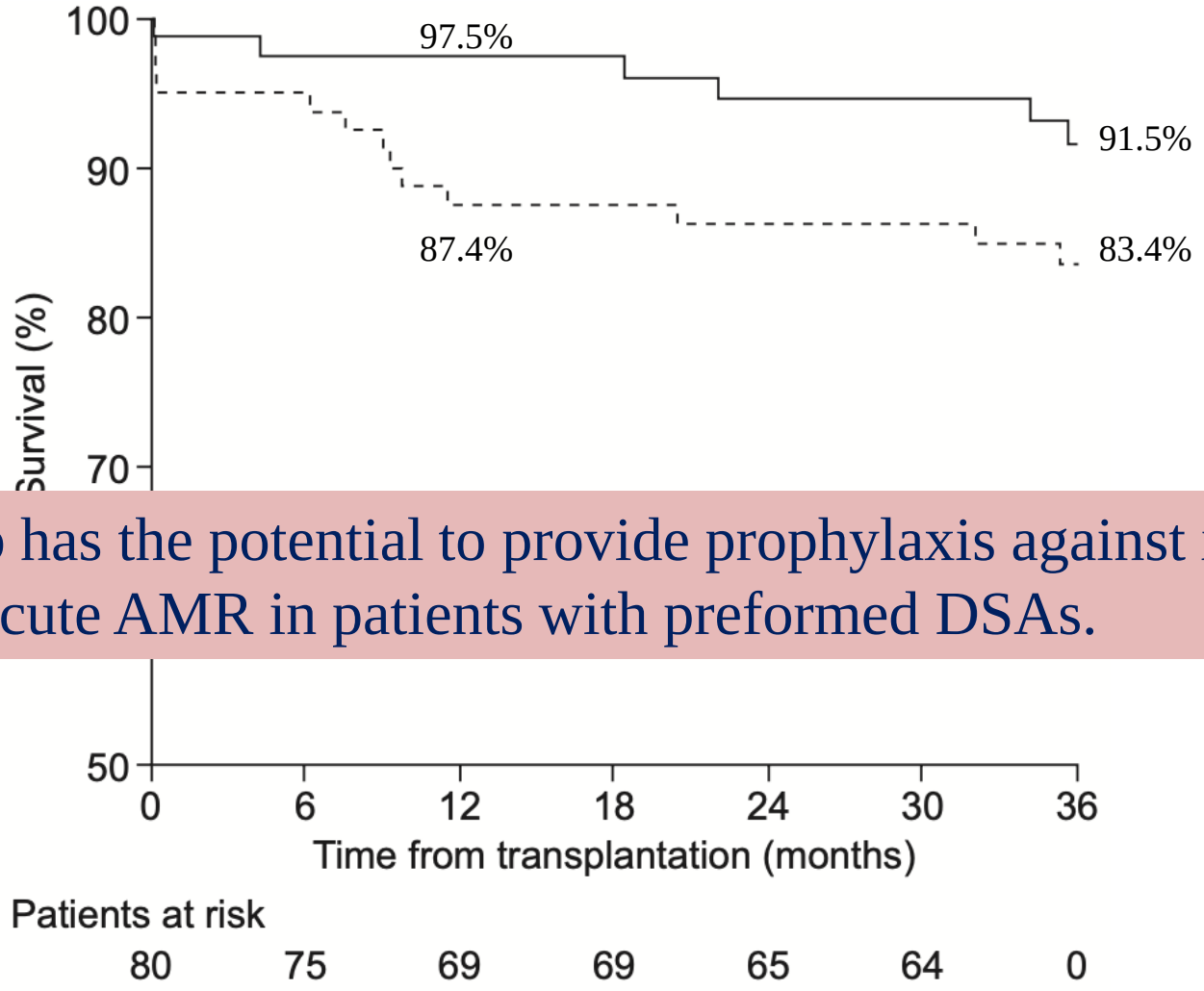


	Transplantation		Induction phase				Maintenance phase				
Week			1	2	3	4	5	6	7	8	9
Day	0	1	7	14	21	28					
Eculizumab dose, mg	1200	900	900	900	900	900	1200	0	1200	0	1200

Am J Transplant. 2019;19:2865–2875.

End point	Week 9 (N = 80) Treated patients, n (%)	Exact 95% CI, *P* value[c]	Month 12 (N = 80) Treated patients, n (%)	Exact 95% CI
Central pathology				
Treatment failure				
Yes	7 (8.8)	3.6-17.2, <.001	15 (18.8)	10.9-29.0
No	73 (91.3)		65 (81.3)	
Composite end point component[a]				
Biopsy-proved acute AMR[d]	3 (3.8)		5 (6.3)	
Graft loss	4 (5.0)		10 (12.5)	
Death	1 (1.3)		2 (2.5)	
Loss to follow-up[b]	0 (0.0)		0 (0.0)	
Local pathology				
Treatment failure				
Yes	11 (13.8)	7.1-23.3, <.01	21 (26.3)	17.0-37.3
No	69 (86.3)		59 (73.8)	
Composite end point component[a]				
Biopsy-proved acute AMR[d]	7 (8.8)		12 (15.0)	
Graft loss	4 (5.0)		10 (12.5)	
Death	1 (1.3)		2 (2.5)	
Loss to follow-up[b]	0 (0.0)		0 (0.0)	

[c]*P* value refers to the comparison between the observed treatment failure rate and the 40% treatment failure rate estimated for patients receiving standard of care from a literature search.
[d]Banff 2007 grade II or grade III AMR detected in "for-cause" biopsies.

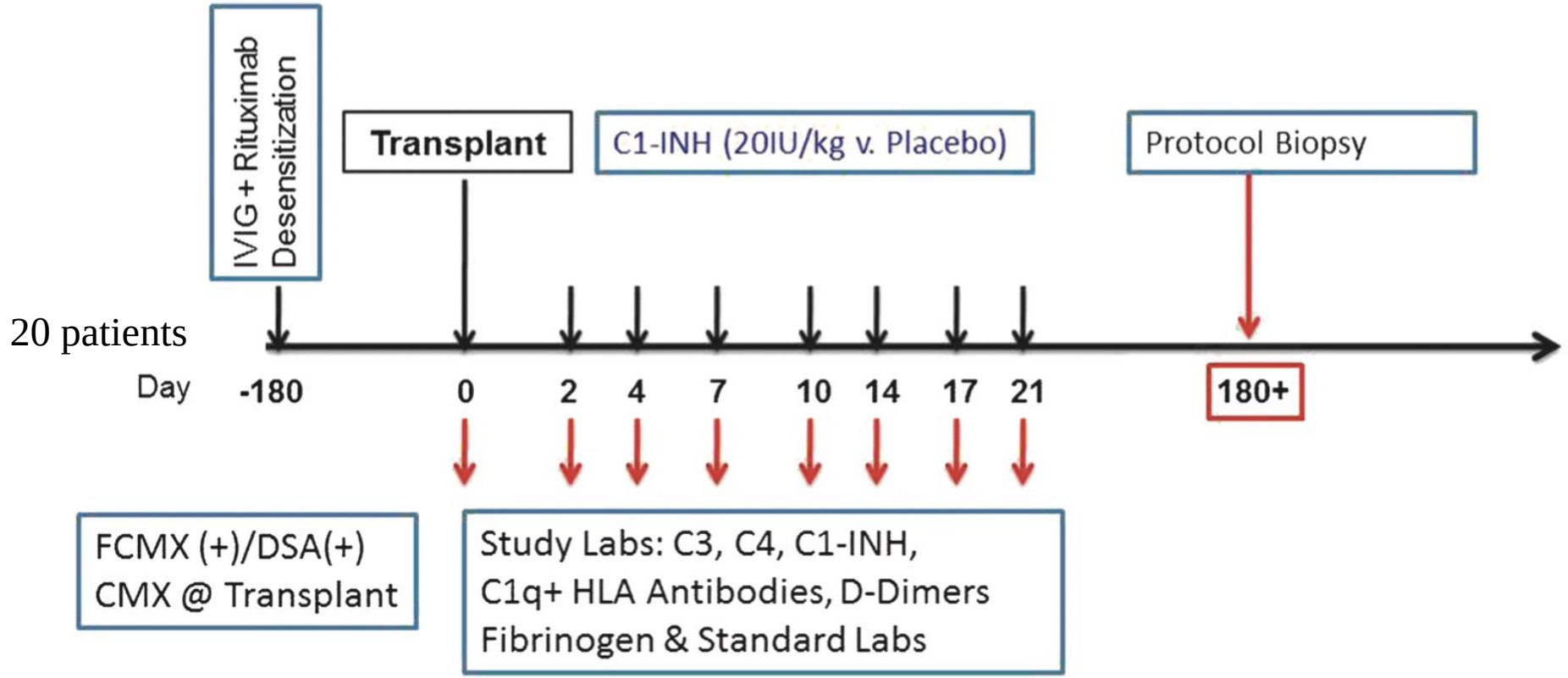


Eculizumab has the potential to provide prophylaxis against injury caused by acute AMR in patients with preformed DSAs.

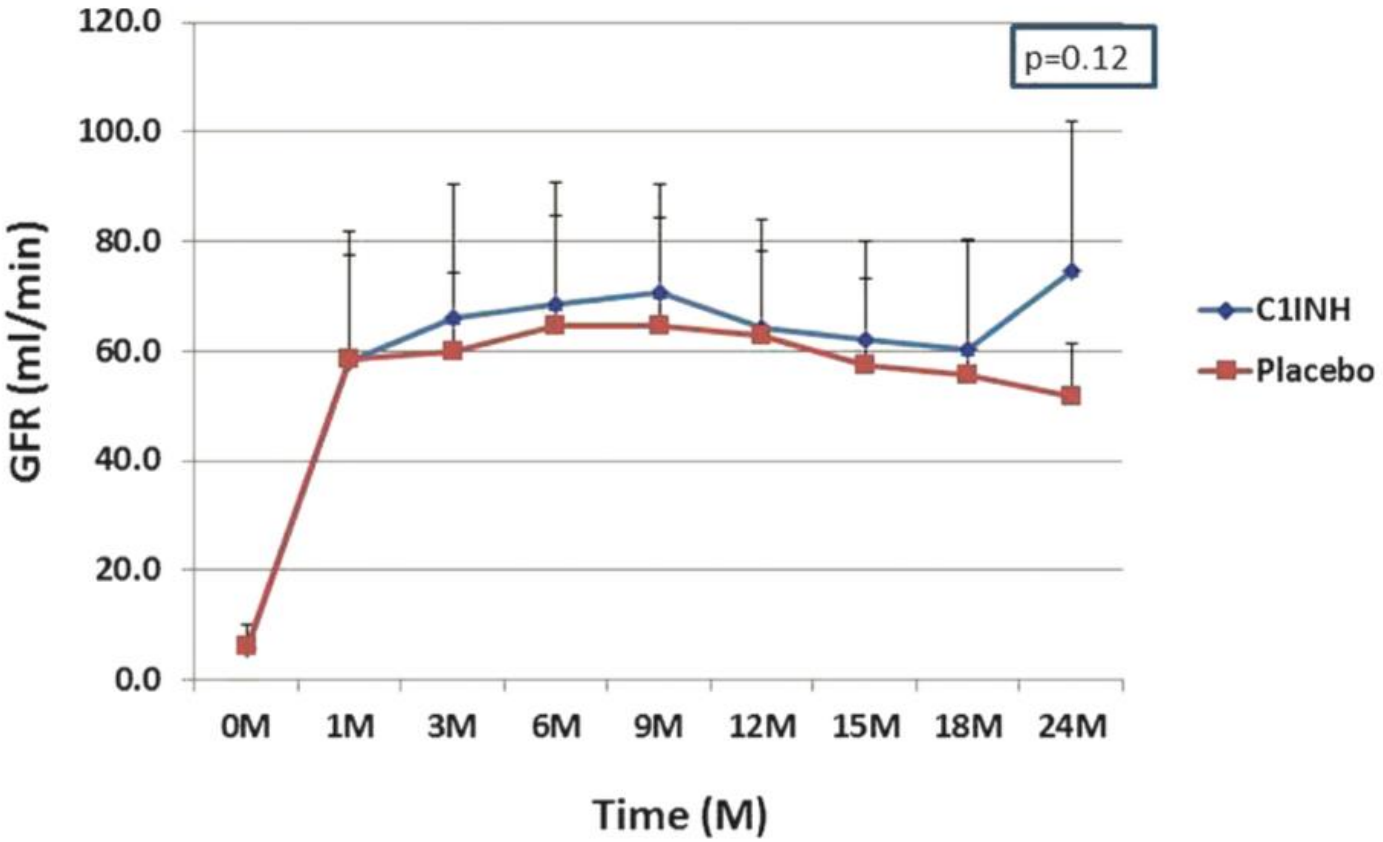
Am J Transplant. 2019;19:2865–2875.

- Pathways “proximal” to C5 might be responsible for subclinical and chronic injury in allograft patients treated with Eculizumab.

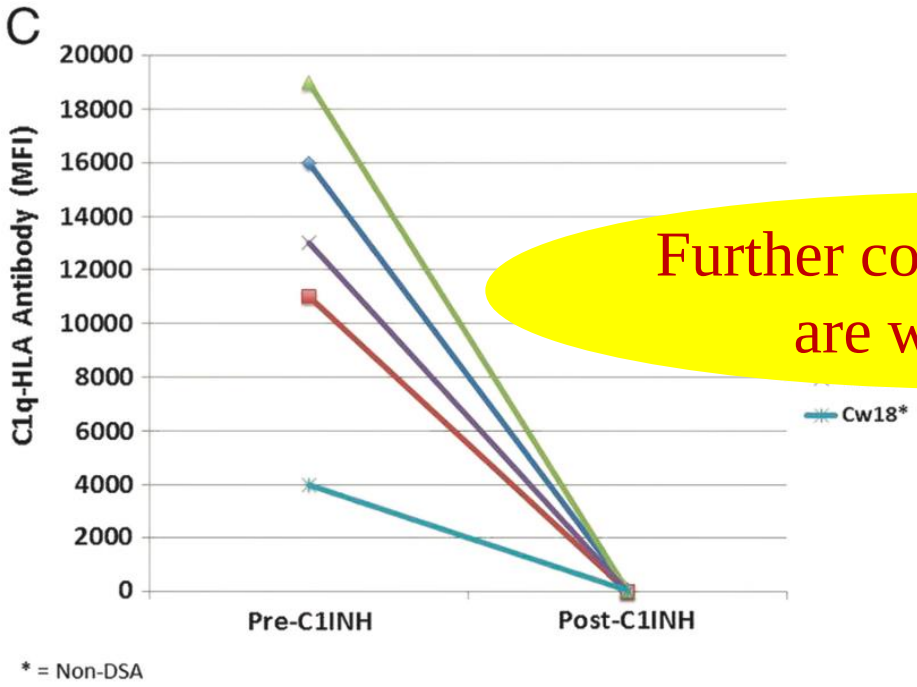
A Phase I/II Placebo-Controlled Trial of C1-Inhibitor for Prevention of Antibody-Mediated Rejection in HLA Sensitized Patients

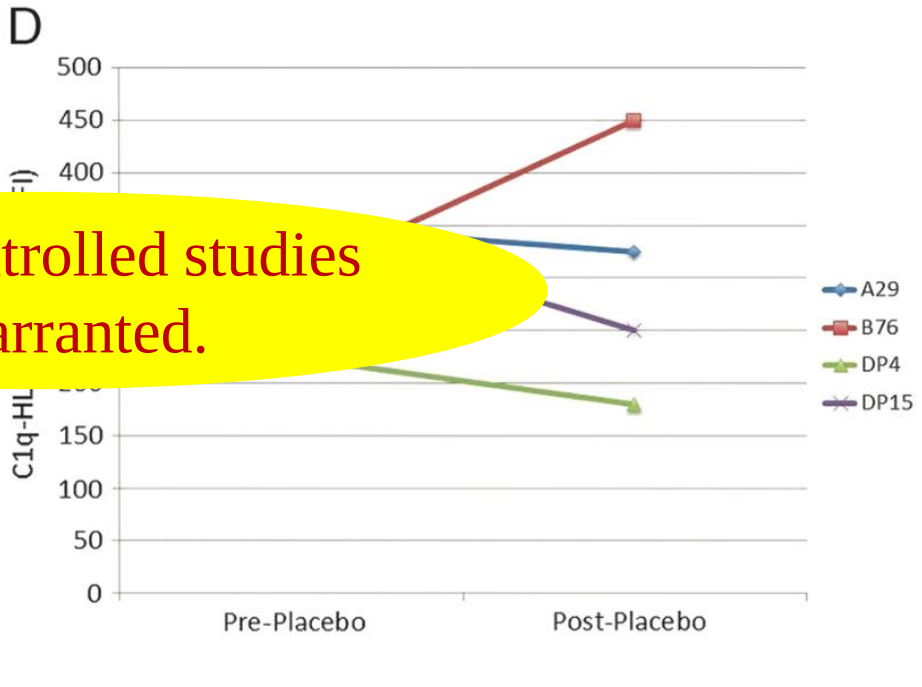


(*Transplantation* 2015;99: 299–308)



(*Transplantation* 2015;99: 299–308)





Further controlled studies are warranted.

No C1-INH patient developed AMR during the study.
The C1-INH appears safe in the posttransplant period.
The C1-INH treatment may reduce IRI. (1 vs 4)
The C1-INH also resulted in reduced C1q+ HLA antibodies.

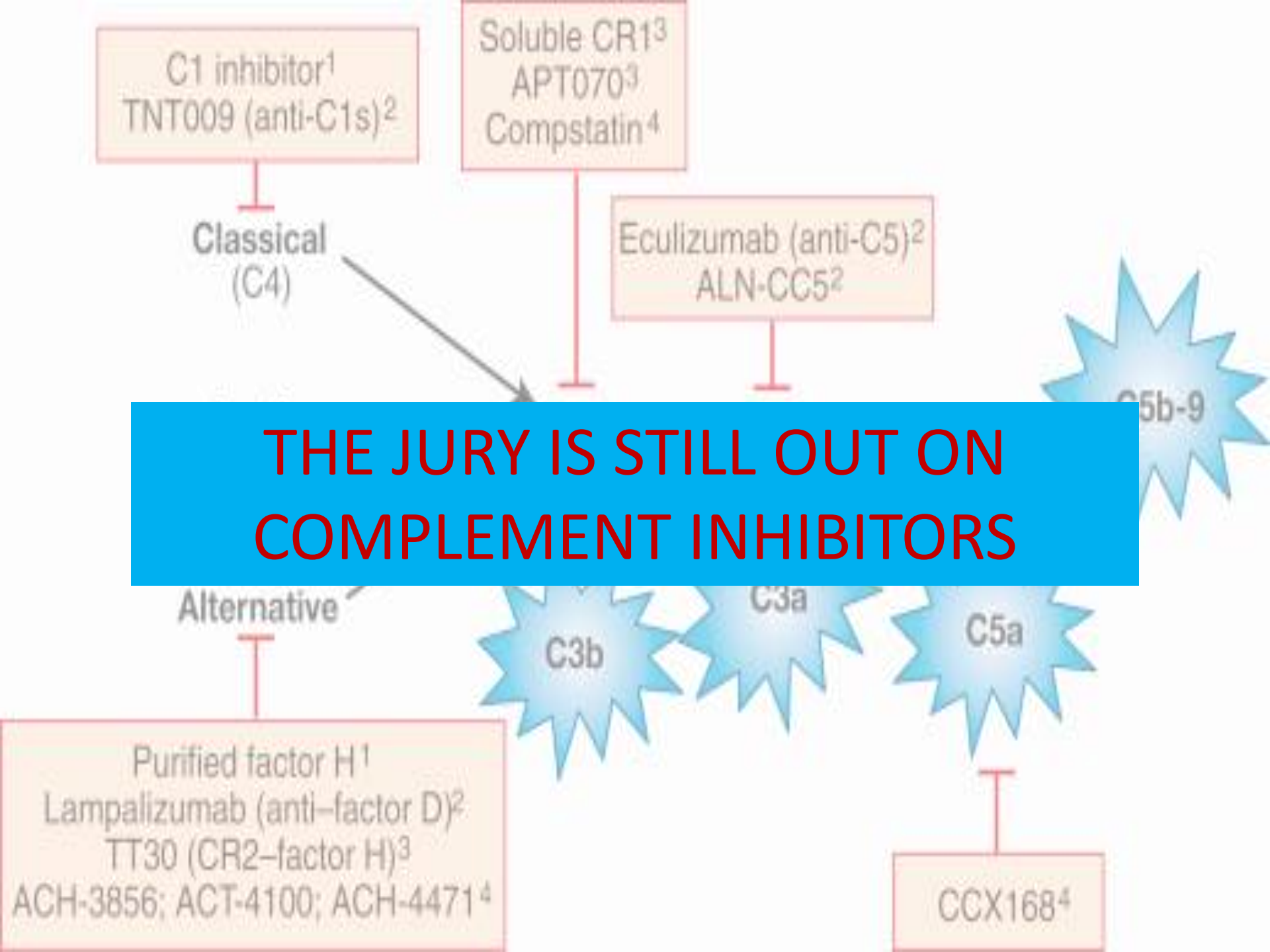
(*Transplantation* 2015;99: 299–308)

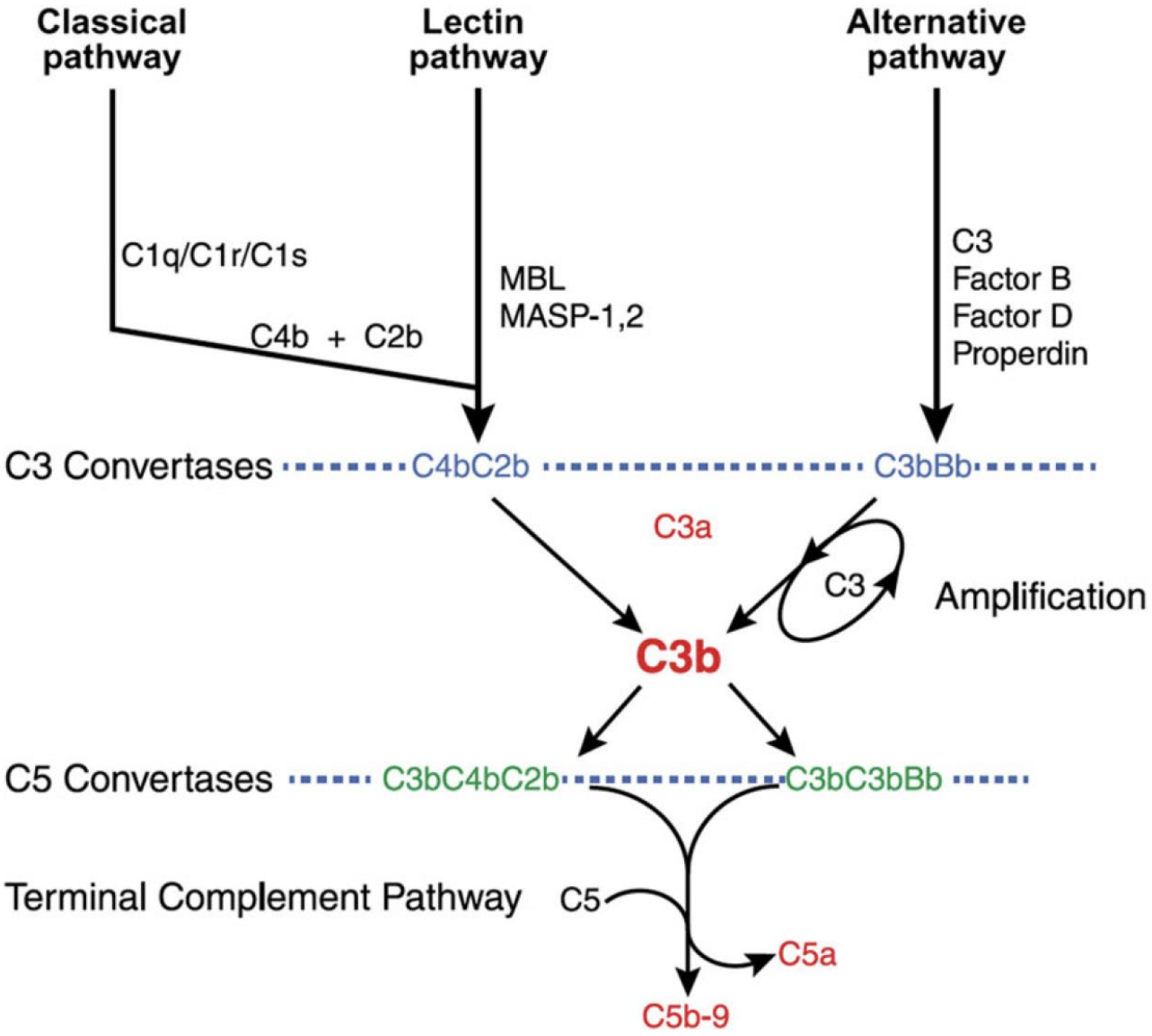
SUMMARY

- We are at the beginning of the way to use complement inhibitors in kidney transplantation, but based on available data we could conclude that:
- C1 inhibitors, unlike Eculizumab, seem to affect the outcome of DGF positively.
- C1 inhibitors, and may be Eculizumab, seem to affect the late outcomes of AMR positively.
- Both C1 inhibitors and Eculizumab showed promising results in prevention of AMR among sensitized patients.


I HEAR THE
JURY'S
STILL OUT ON
COMPLEMENT
INHIBITORS


Thank you
مرکز پژوهشی آموزشی و درمانی


C1 inhibitor[1]
TNT009 (anti-C1s)[2]
Soluble CR1[3]
APT070[3]
Compstatin[4]
Classical
(C4)
Eculizumab (anti-C5)[2]
ALN-CC5[2]
C5b-9
THE JURY IS STILL OUT ON COMPLEMENT INHIBITORS
Alternative
C3b
C3a
C5a
Purified factor H[1]
Lampalizumab (anti–factor D)[2]
TT30 (CR2–factor H)[3]
ACH-3856; ACT-4100; ACH-4471[4]
CCX168[4]



British Medical Bulletin, 2017, **124**:5–17

Complement Inhibitors

Name(s)	Structure	Major targets	Complement Pathways inhibited*
C1 INH (Berinert, Cinryze, Ruconest)	Natural or Recombinant Glycoprotein	C1r, C1s, MASPs	C, L,
Nafamostat (FUT-175)	Synthetic guanidinobenzoate (broad spectrum low molecular weight serine protease inhibitor)	C1r, C1s, MASPs, B, D, C2	A, C, L
Compstatin	Synthetic 13 residue cyclic peptide	C3 and C5 convertase	A, C, L
Mirococept/TP-10	Recombinant soluble analogs of type 1 complement receptor	C3b, C3 and C5 convertases	A, C. L
Eculizumab (Soliris)	Humanized monoclonal antibody	C5	A, C, L

A indicates alternate; C, classic; L, lectin.

(*Transplantation* 2016;100: 1415–1424)

Drug	Description of the drug	Mechanism of action	Phase of clinical development
sCR1, TT10	Soluble form of recombinant CR1	Inactivation of C3b	Inconclusive results in cardiac surgery and in dense deposit disease
APT070, Mirococept	Truncated CR1 with lipopeptide membrane	Inactivation of C3b	Clinical trial for preventing ischemia-reperfusion injury in the kidney allograft
TT30 (Alexion)	Fusion protein between CCP1-4 FH and CCP1-4 CR2	Inactivation of C3b	Preclinical
Mini FH (Amyndas)	Fusion protein between CCP1-4 FH and CCP19-20FH	Inactivation of C3b	Preclinical
r FH (Optherion)	Purified or recombinant FH	Inactivation of C3b	Preclinical
Berinert (CSL Behring), Cinryze (ViroPharma)	Purified or recombinant C1 inhibitor	Inactivation of C1	Drug approved for hereditary angioedema, clinical trial in Trx
Eculizumab (Alexion)	Humanized monoclonal IgG2/4 antibody against C5	Inhibition of the cleavage of C5 to C5a and C5b	Drug approved for PNH, aHUS; clinical trials in complement-mediated diseases
Lampalizumab (Roche)	Humanized monoclonal antibody directed against factor D	Inhibition of Factor B cleavage within the C3bB	Clinical trial in age macular degeneration (Phase 2)
AMY-101 or Cp40 (Amyndas)	Derived product from compstatin: Cyclic peptide that binds C3	Inhibition of the C3 cleavage by the C3 convertase	Preclinical
CCX168 (ChemoCentryx)	Small-molecule antagonist of human C5aR/CD88,	C5a inhibition	Clinical trial in ANCA-associated renal vasculitis
OMS872 (Omeros)	Humanized monoclonal antibody again MASP 2	Inhibition of C4 cleavage	Clinical trial in atypical bleHUS (Phase 2)
ALN-CC5 (Alnylam)	RNAi therapeutic targeting C5	Inhibition of the C5 synthesis by the liver	Preclinical

Kidney International (2015) **88,** 967–973; doi:10.1038/ki.2015.253;

Table 2 | Current clinical trials of eculizumab and C1-esterase inhibitors in kidney transplantation

Eculizumab

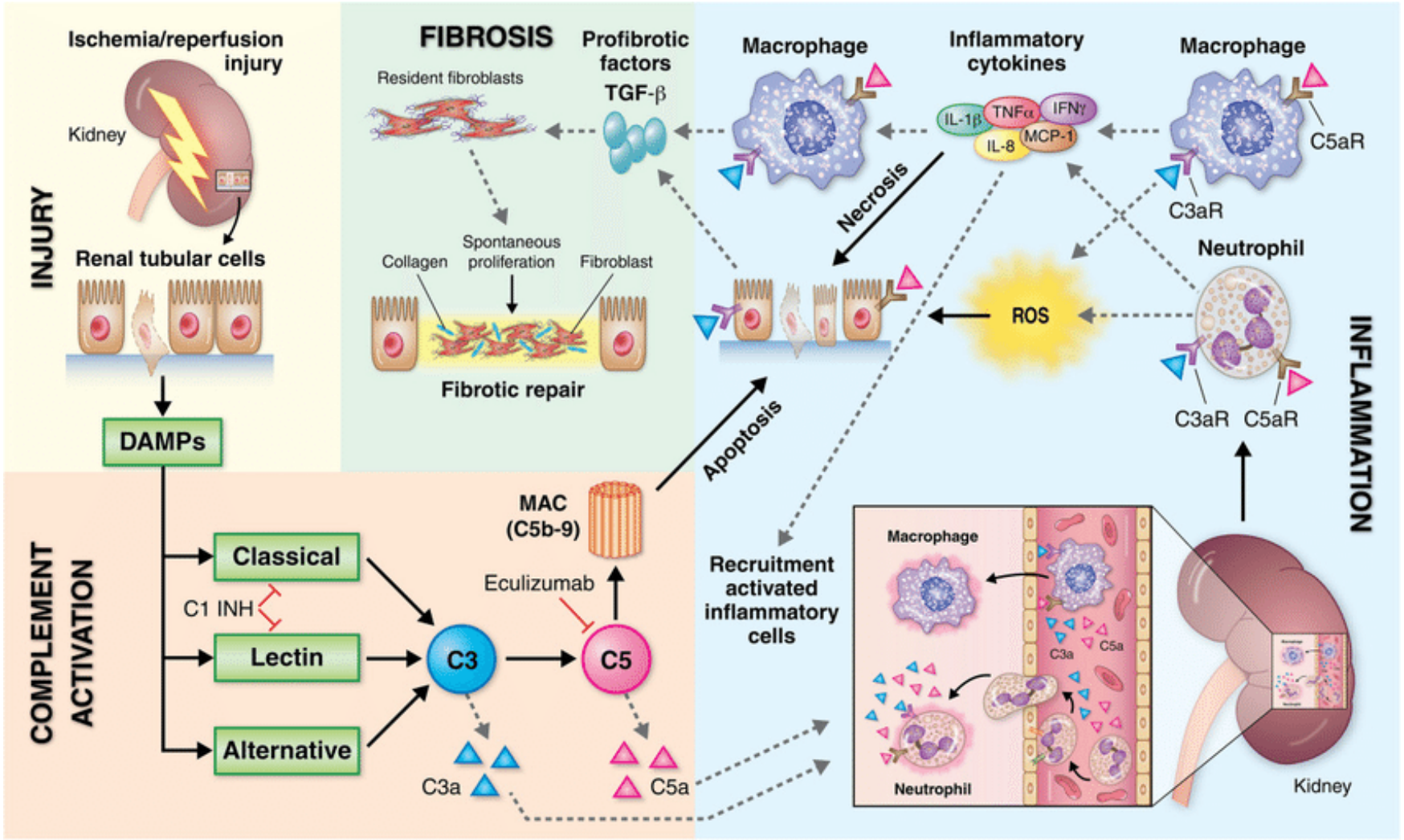
- Prevention of delayed graft function (compared with placebo: NCT01756508, NCT01919346, NCT02134314, NCT01403389)
- Prevention of acute clinical antibody-mediated rejection:
  - In living donor kidney transplantation (NCT01399593): patients have been desensitized according to local practice (IVIg, plasma exchange) but without anti-CD20 and then randomized to receive either local practice treatment (IVIg, plasma exchange) or eculizumab for 9 weeks
  - In deceased donor kidney transplantation (NCT01567085): kidney transplant recipients with anti-HLA donor-specific antibodies (peak or day-0 serum >3000 MFI) have been given eculizumab for 9 weeks without any control group
- Treatment of acute antibody-mediated rejection (NCT01895127): a randomized open label trial comparing eculizumab with plasma exchanges and IVIg in the treatment of acute ABMR
- Treatment of subclinical antibody-mediated rejection (NCT02113891). Study withdrawn
- Treatment of chronic antibody-mediated rejection (NCT01327573): a randomized open label trial comparing eculizumab with regular immunosuppression
- Prevention of recurrence in:
  - C3 glomerulopathy (NCT01221181, NCT02093533): a single-arm study testing the efficacy of eculizumab to treat recurrence of dense deposit disease and C3 glomerulopathy
  - Antiphospholipid syndrome (NCT01029587): a phase 2 study to prevent thrombosis of the kidney transplant in patients with a catastrophic antiphospholipid antibody syndrome
- ABO-incompatible transplantation (NCT01095887): an open label trial aiming at preventing ABMR in ABO-incompatible living donor kidney transplant recipients

C1 esterase inhibitor

- Prevention of delayed graft function (NCT02134314)
- Use of human C1 esterase inhibitor to treat acute ABMR (NCT01147302)
- Safety and tolerability of Berinert to prevent rejection (NCT01134510)

Abbreviations: ABMR, antibody-mediated rejection; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin; MFI, mean fluorescent intensity.

Kidney International (2015) **88,** 967–973; doi:10.1038/ki.2015.253;



Fibrogenesis & Tissue Repair 2014, **7**:16

TABLE 2.

Trials of C1 INH in transplantation listed in clinicaltrials.gov[a]

Title	Phase	NCT Number	Type	Sponsor	Status
C1 INH Preoperative and post-kidney transplant to prevent DGF and IRI	I	02134314	R, PC, DB	Cedars-Sinai Medical Center, Los Angeles, CA	Recruiting
Safety and tolerability of Berinert (C1 inhibitor) therapy to prevent AMR in HLA sensitized kidney transplant recipients	I	01134510	R, PC, DB	Cedars-Sinai Medical Center	Completed[67]
Recombinant human C1 INH for the treatment of early AMR in renal transplantation	II	01035593	R, OL	Shire, Lexington, MA	Withdrawn[b]
A pilot study to evaluate the use of C1 INH (human) in patients with acute (kidney) AMR	II	01147302	R, PC, DB	Shire, Lexington, MA	Completed[68]
Combined drug approach to prevent IRI during transplantation of livers	I	01886443	SB	Universitaire Ziekenhuisen Leuven, Belgium	Completed
Combined drug approach to prevent IRI during transplantation of livers (CAPITL)	II	02251041	R, SB	Universitaire Ziekenhuisen Leuven, Belgium	Recruiting
Cinryze as a donor pretreatment strategy in kidney recipients of KDPI>85% organs	I	02435732	R, PC,	University of Wisconsin Madison, WI	Not yet recruiting

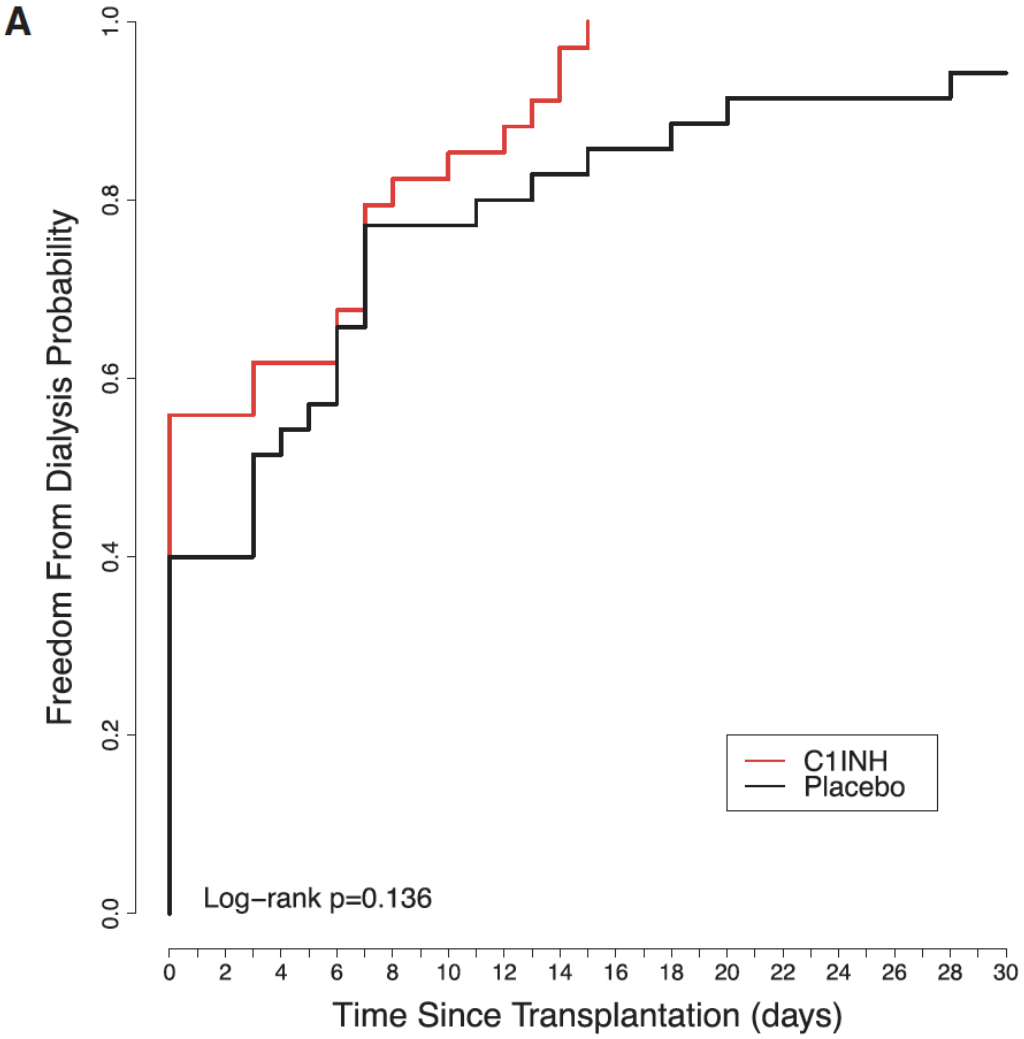
[a] No trials are listed in EUdraCT which are not listed here.
[b] Sponsor's comment: "Withdrawn due to Improvements in Clinical Practice (which) Have Reduced The Apparent Incidence of AMR."
R indicates randomized; PC, placebo controlled; DB, double blinded; SB, single blinded (subject); OL, open label.

(*Transplantation* 2016;100: 1415–1424)

Table 2 | Selected registered randomized and controlled DGF trials in ClinicalTrials.gov (accessed 3 September 2013)[a]

Intervention	Target	Primary end point(s)	Stage and estimated enrollment	ClinicalTrials.gov identifier
I5NP	siRNA inhibiting p53	Safety and incidence of delayed kidney graft function	Phase 2B $N = 366$	NCT00802347
Eculizumab	Complement C5a	Hemodialysis (7 days post-transplantation)	Phase 2 $N = 24$	NCT01919346
OPN-305	TLR2	Hemodialysis (7 days post-transplantation)	Phase 2 $N = 278$	NCT01794663
BB3	Hepatocyte growth factor/scatter factor	Difference in creatinine clearance over time	Phase 2 $N = 36$	NCT01561599
Remote ischemic preconditioning	Multiple	Number of organs recovered per donor	Phase 3 $N = 320$	NCT01515072
Hypothermia	Multiple	Feasibility/safety; recipient organ function	Phase 2 $N = 60$	NCT01544530
Alteplase	Dissolution of microthrombi by *ex-vivo* treatment of DCD organs with rTPA	Delayed kidney graft function and primary liver graft non-function	$N = 135$	NCT01197573
Etanercept	TNF-α inhibitor to the perfusion fluid	Hemodialysis (7 days post-transplantation)	Phase 2 $N = 100$	NCT01731457

Abbreviations: DGF, delayed graft function; siRNA, small interfering RNA; TLR, Toll-like receptor; TNF, tumor necrosis factor.
[a]Excluding trials testing preservation solutions and machine perfusion.



Am J Transplant. 2018;18:2955–2964.

- C1 inhibitors, unlike Eculizumab, seem to affect the outcome of DGF positively.

- The ongoing trials (NCT02435732; NCT03791476) would shed a light on their efficacy in prevention of DGF.

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Trials of C1 INH in transplantation listed in clinicaltrials.gov[a]

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Cinryze as a donor pretreatment strategy in kidney recipients of KDPI>85% organs	I	02435732	R, PC,	University of Wisconsin Madison, WI	Not yet recruiting

[a] No trials are listed in EUdraCT which are not listed here.
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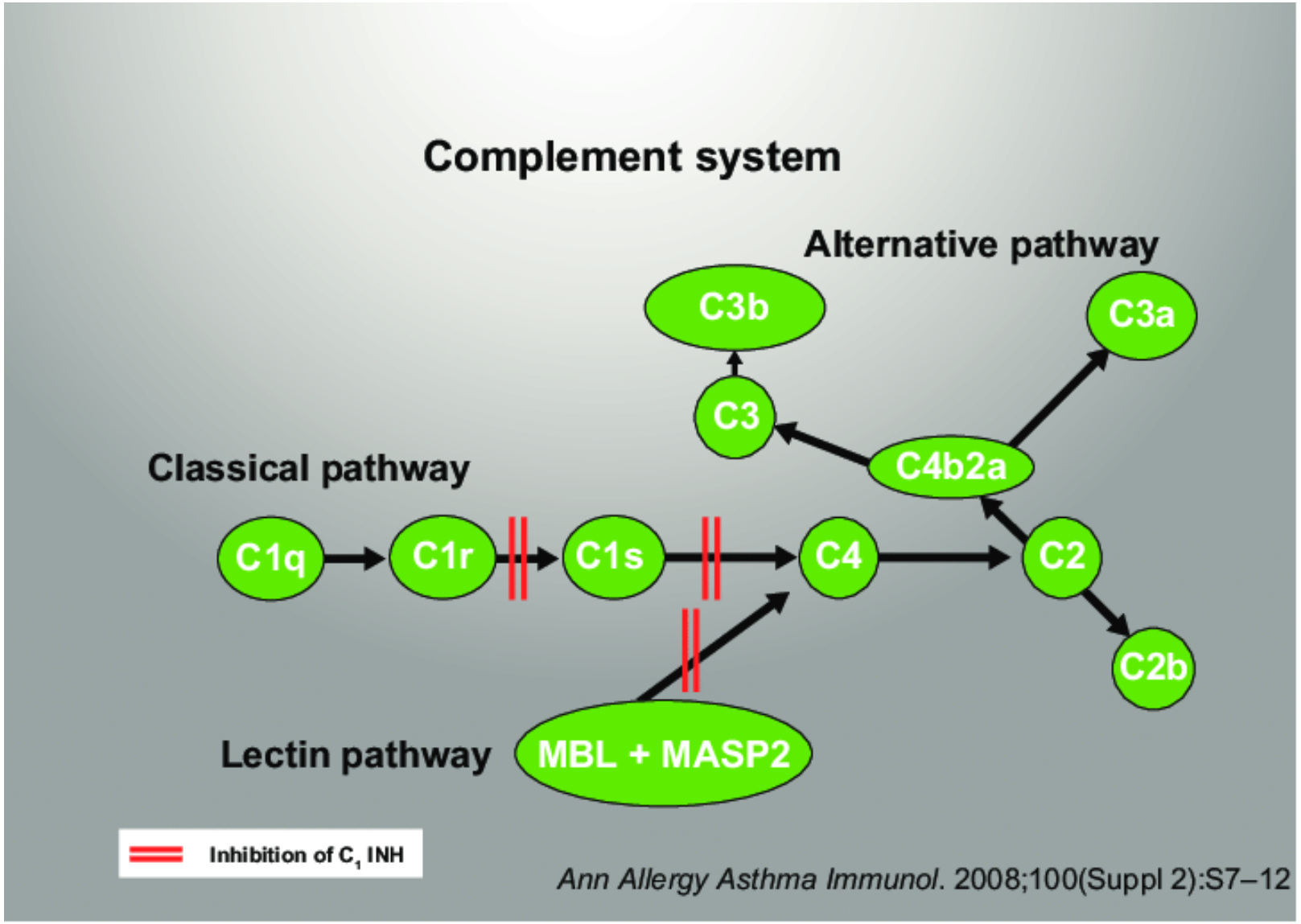
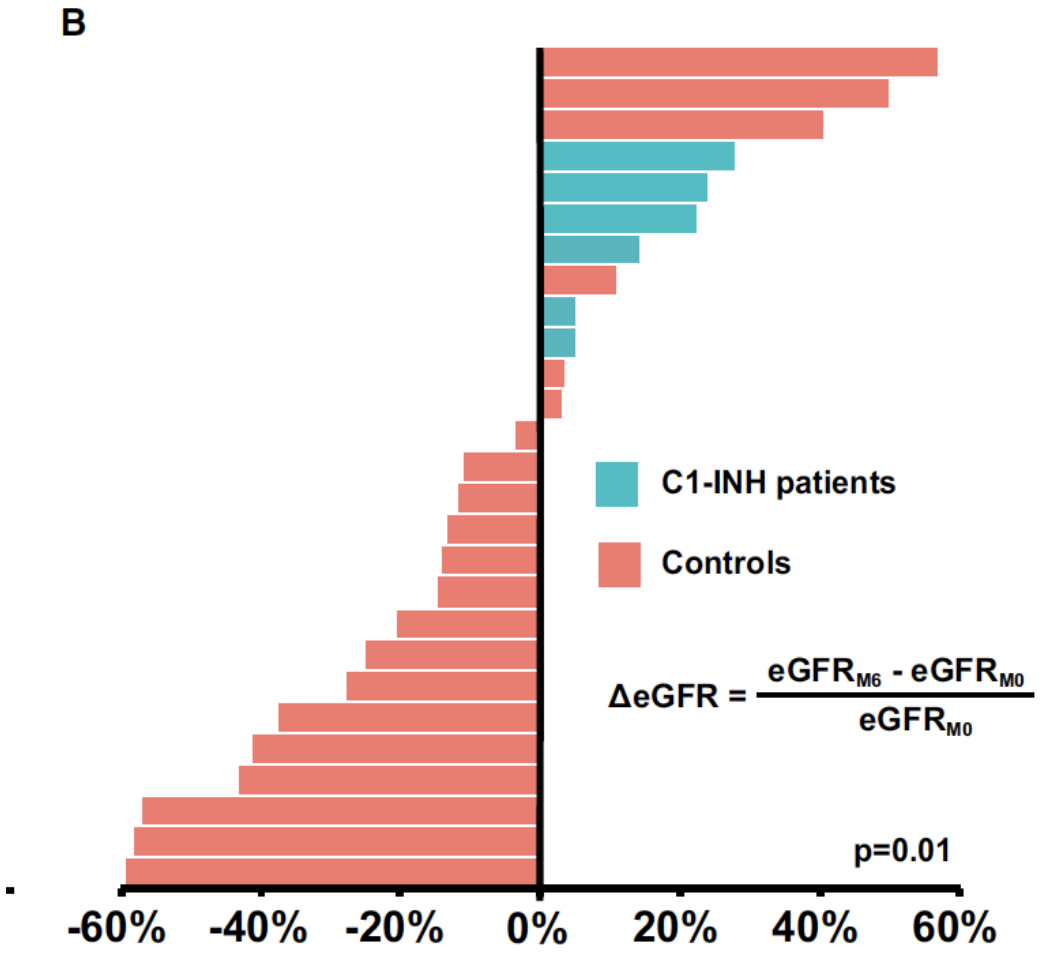
(*Transplantation* 2016;100: 1415–1424)


Complement system
Alternative pathway
C3b
C3a
C3
C4b2a
Classical pathway
C1q
C1r
C1s
C4
C2
C2b
Lectin pathway
MBL + MASP2
Inhibition of C1 INH
Ann Allergy Asthma Immunol. 2008;100(Suppl 2):S7–12



American Journal of Transplantation 2016; 16: 1596–1603

	Trial	Status
NCT02113891	**Eculizumab Therapy for Subclinical Antibody-mediated Rejection in Kidney Transplantation (TAMARCIN)**	Withdrawn
NCT01895127	**Efficacy and Safety of Eculizumab for Treatment of Antibody-mediated Rejection Following Renal Transplantation**	Terminated due to lack of efficacy
NCT01035593	**Recombinant Human C1 Inhibitor for the Treatment of Early Antibody-Mediated Rejection in Renal Transplantation**	Withdrawn
NCT02547220	**A Multicenter Study to Evaluate the Efficacy and Safety of Cinryze® for the Treatment of Acute Antibody-mediated Rejection in Participants With Kidney Transplant**	Terminated due to lack of efficacy

Clinicaltrials.gov (Accessed November 6,2019)

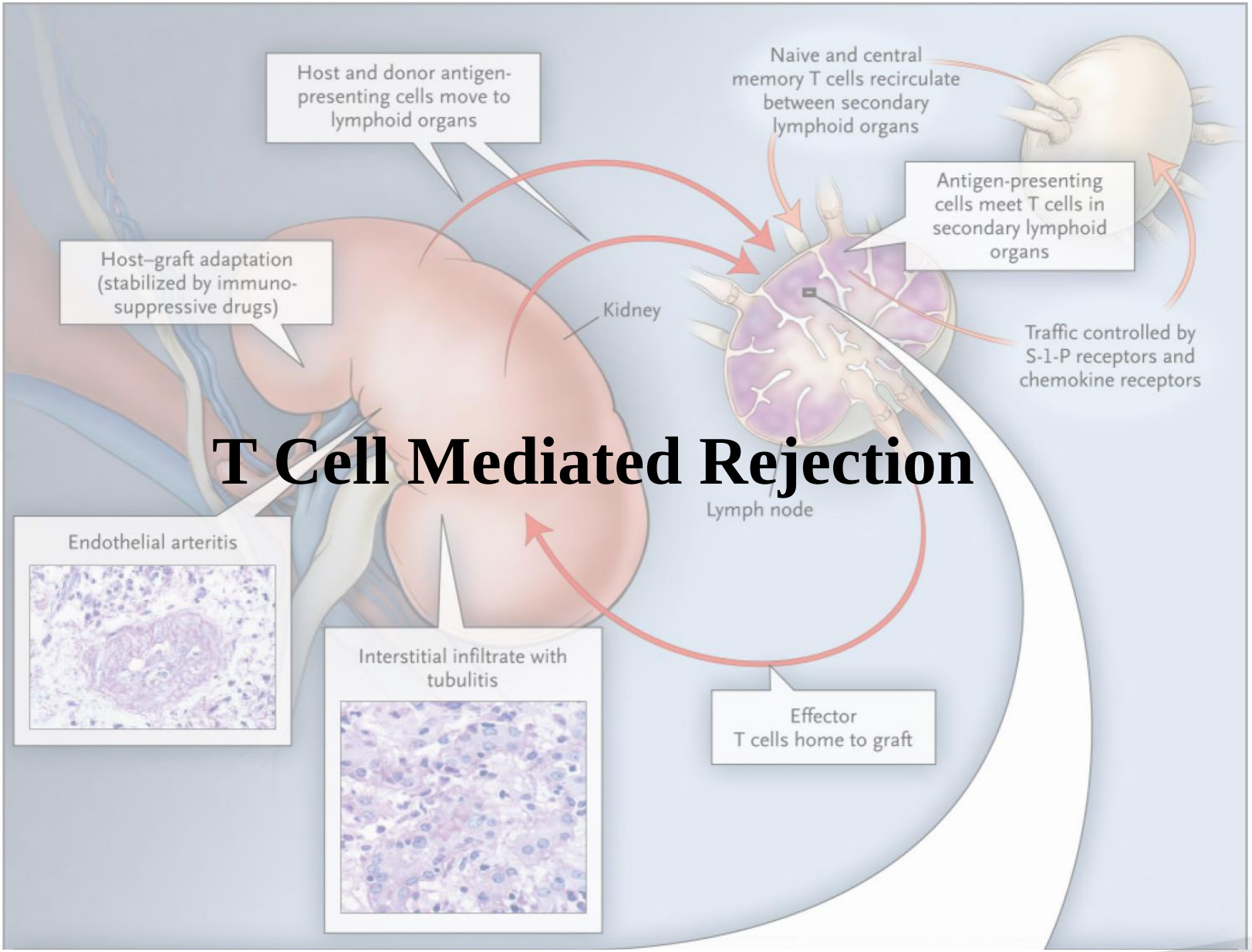
Early Subclinical Alloantibody-Associated Injury in Positive Crossmatch Kidney Transplantation (+XMKTx) Despite Terminal Complement Blockade.: Abstract# 703

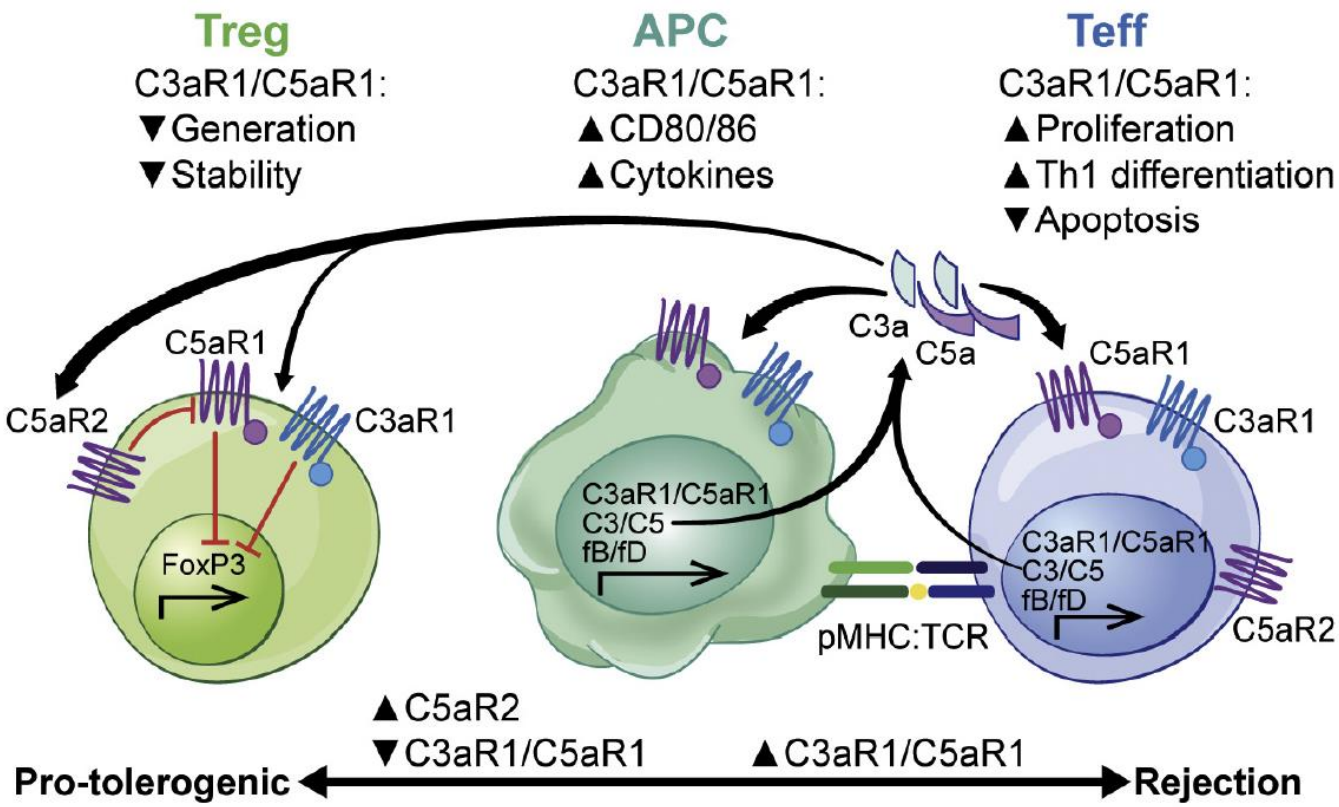
Dean, P.; Park, W.; Cornell, L.; Schinstock, C.; Stegall, M.

Transplantation: July 15, 2014 - Volume 98 - Issue - p 79

- AMR in the first 3 months was lower in the EC group than the PE-alone group (6.7% vs. 43.8%, $p<0.01$).
- During EC treatment, well-functioning +XMKTx showed LM evidence of microvascular inflammation (PTC score >1) at 1 month (10%) and 3 months (26.7%).
- These data suggest that microvascular inflammation and endothelial cell activation are independent of C5 and that additional therapies likely will be needed to prevent chronic antibody-associated allograft damage.

T Cell Mediated Rejection





- Direct effect on T-cell proliferation and activity (C3a and C5a, MCP/CD46) (11, 110)
- The influence on T-cell differentiation and regulatory T cell induction (C3a, C5a, C4, C1q, DAF/CD55) (11, 107, 104, 105)
- The influence on monocyte infiltration (C5aR) (100)

Clin Lab Med ■ (2018) ■–■
https://doi.org/10.1016/j.cll.2018.10.004

Complement 5a Receptor Inhibition Improves Renal Allograft Survival

Faikah Gueler,* Song Rong,* Wilfried Gwinner,* Michael Mengel,†‡ Verena Bröcker,†

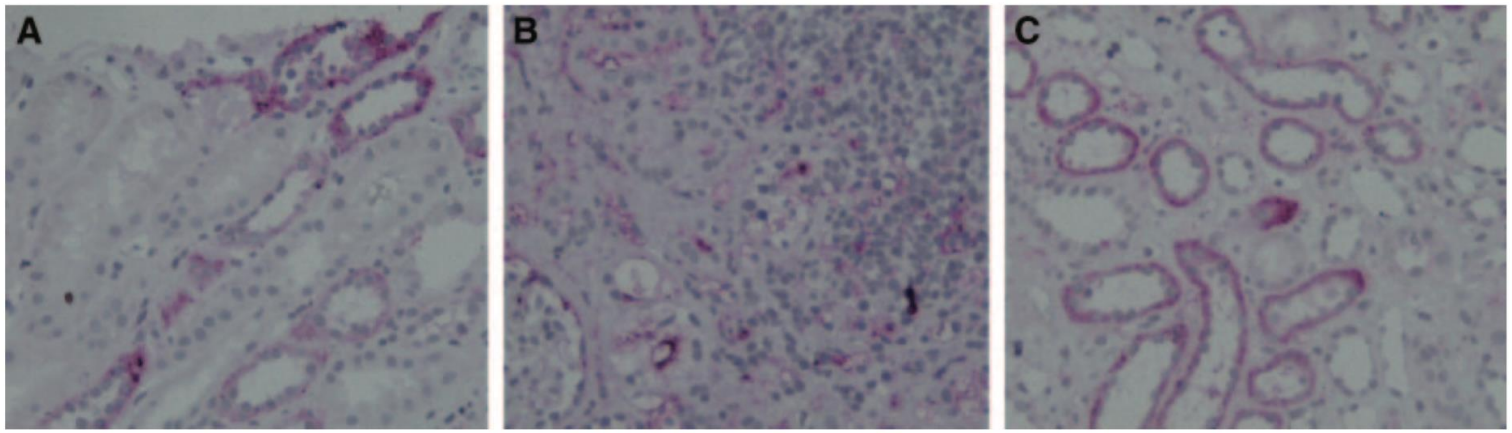
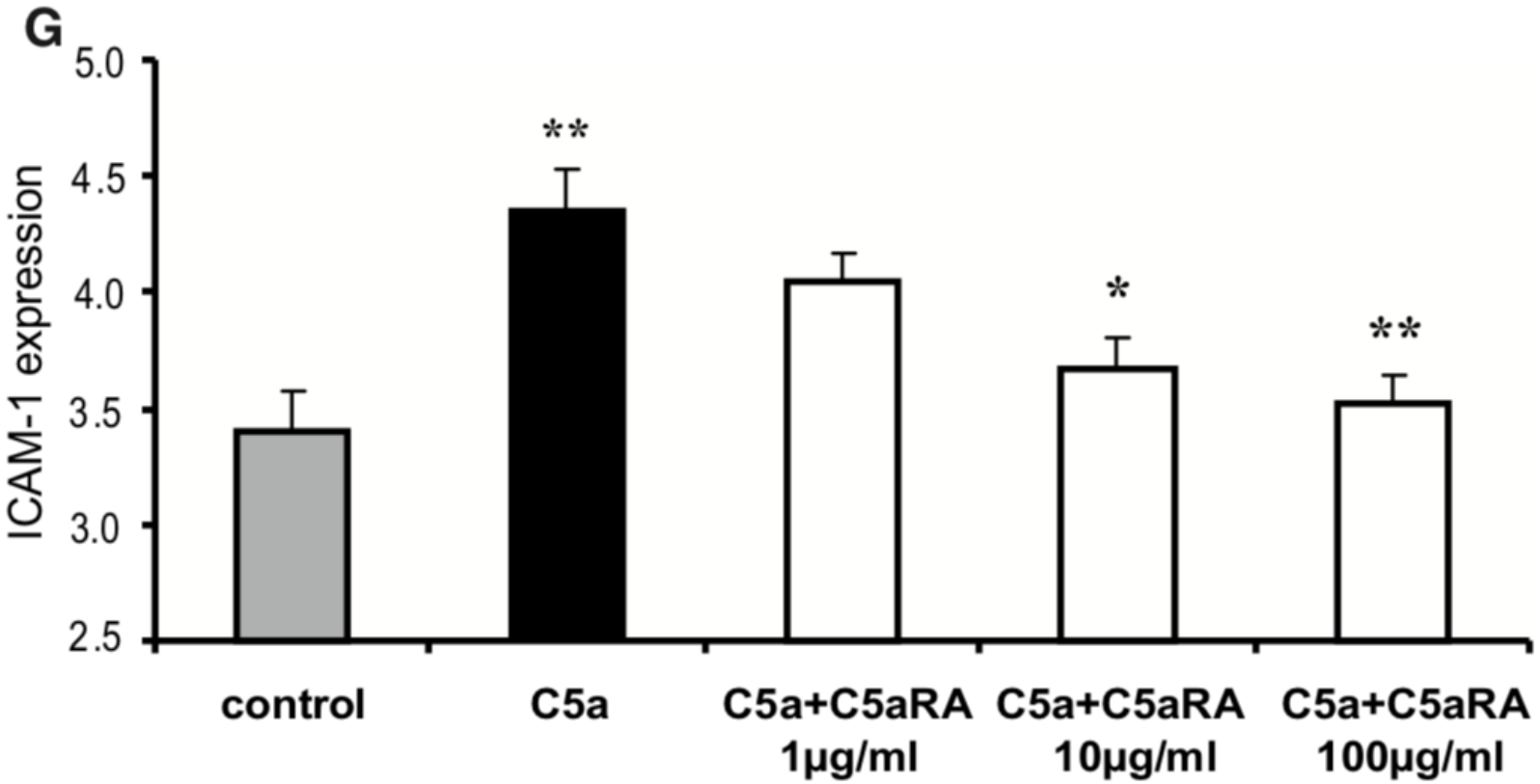


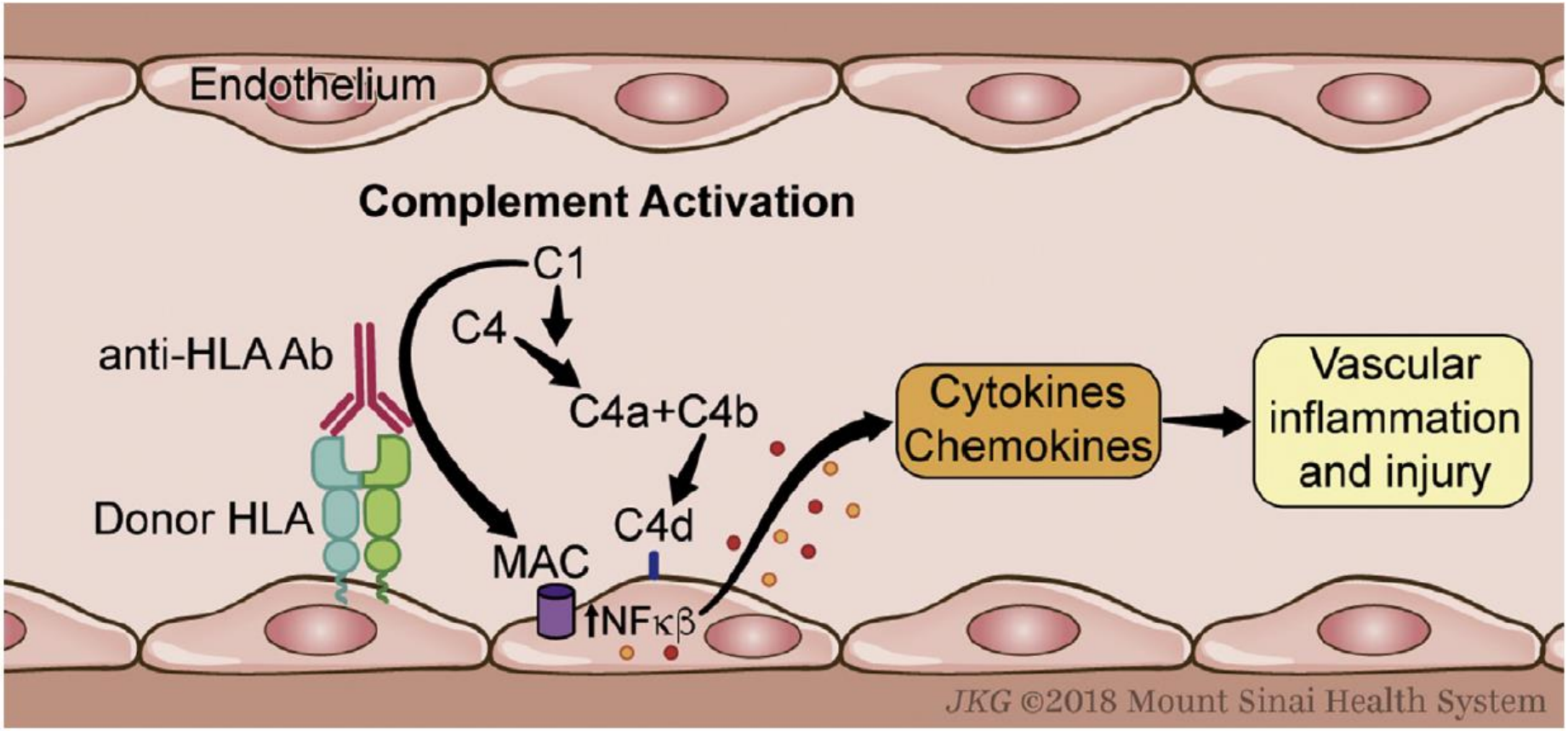
Figure 1. C5aR expression in human renal allograft rejection. (A) C5aR expression in proximal and distal tubuli of normal protocol biopsies. (B) C5aR expression in interstitial infiltrating cells of cases with TCMR Banff Ib. (C) Tubular C5aR expression in cases with IF/TA.

J Am Soc Nephrol 19: 2302–2312, 2008. doi: 10.1681/ASN.2007111267



C5aR blockade markedly reduced alloreactive T cell priming. C5aR plays an important role in mediating acute kidney allograft rejection, suggesting that pharmaceutical targeting of C5aR may have potential in transplantation medicine.

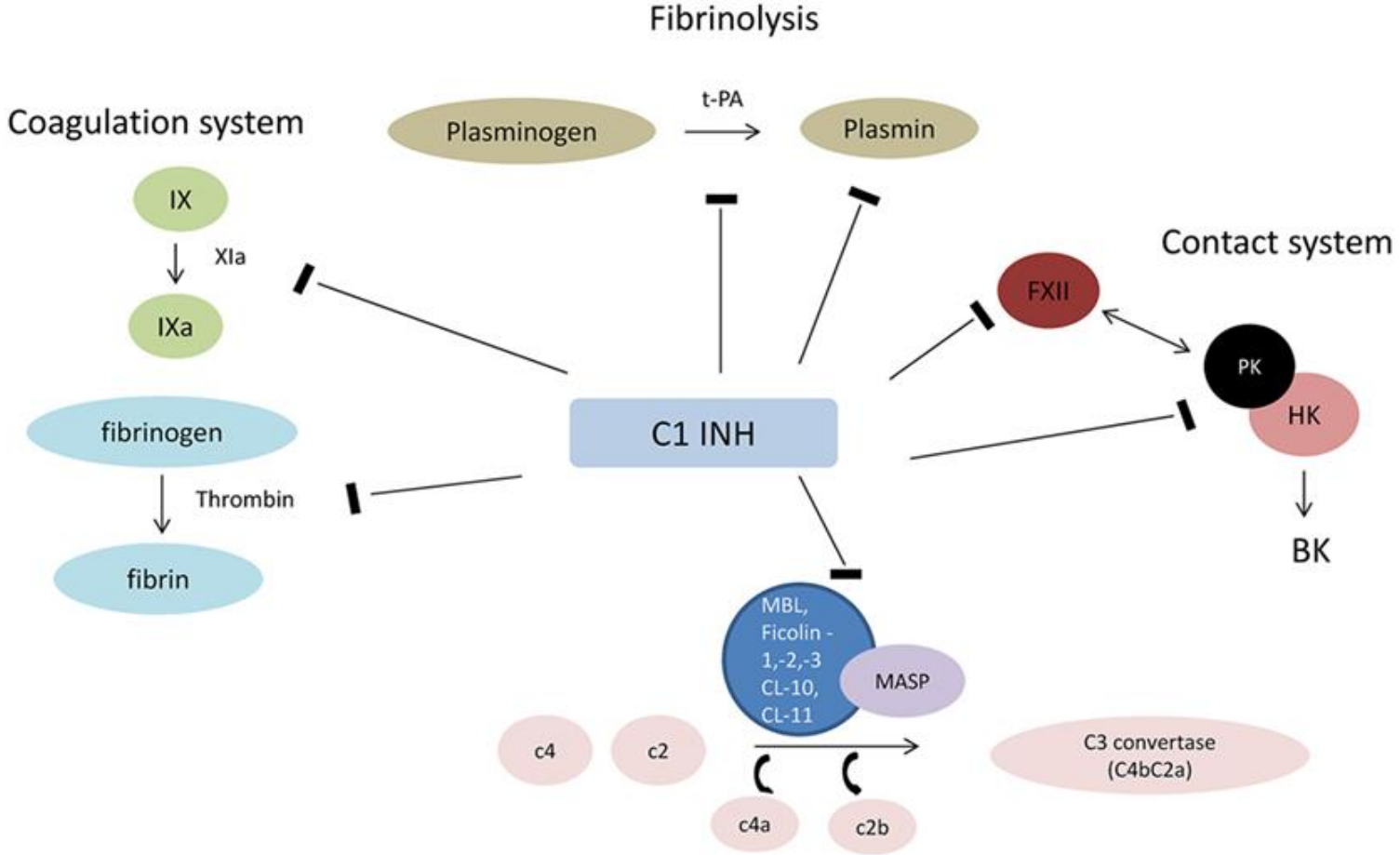
J Am Soc Nephrol 19: 2302–2312, 2008. doi: 10.1681/ASN.2007111267



- Direct effect on cells (MAC) (135)
- Enhancement of T-cell response (MAC) (127)
- Pro-inflammatory stimulation (C3a, C5a) (135)
- The influence on IgG antibody production (CR1, CR2) (124)

Clin Lab Med ■ (2018) ■–■
https://doi.org/10.1016/j.cll.2018.10.004

A Phase I/II Placebo-Controlled Trial of C1-Inhibitor for Prevention of Antibody-Mediated Rejection in HLA Sensitized Patients



(*Transplantation* 2015;99: 299–308)

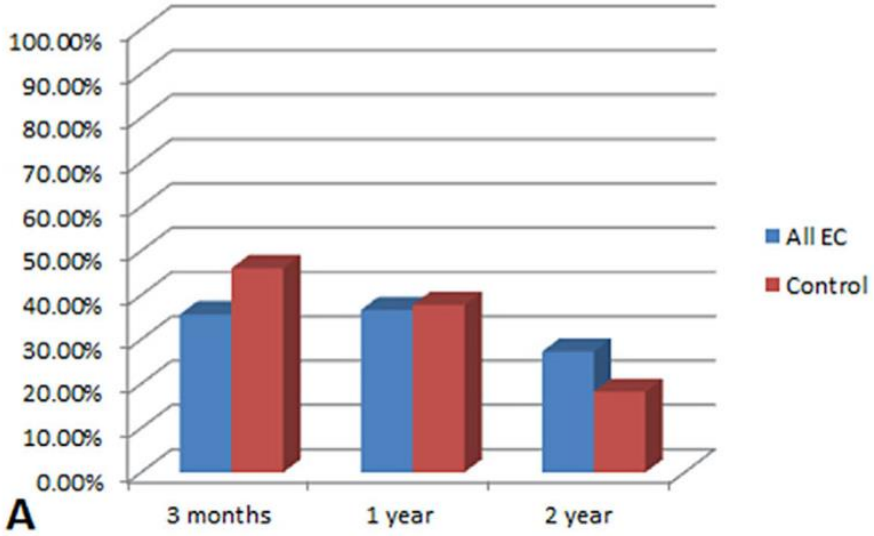
TABLE 4 Primary end point as determined by the central pathologists

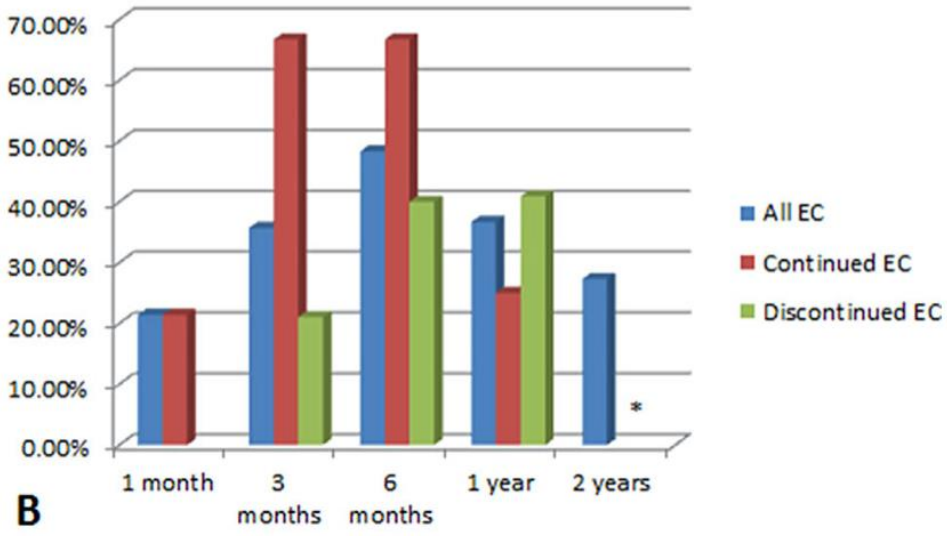
	Eculizumab (N = 51) n (%)	SOC (N = 51) n (%)	Difference (exact 95% CI)	*P* value
Composite primary end point				
Treatment failure rate (including grades II and III AMR)	5 (9.8)	7 (13.7)	−3.9% (−23.9, 16.3)	.760
Composite primary end point components				
Acute AMR (grade II or III)	5 (9.8)	5 (9.8)		
Graft loss	0 (0.0)	3 (5.9)		
Death	1 (2.0)	1 (2.0)		
Loss to follow-up	0 (0.0)	2 (3.9)		

Am J Transplant. 2019;19:2876–2888.

- C1 inhibitors, and may be Eculizumab, seem to affect the late outcomes of AMR positively.

- The ongoing trial (NCT03221842) would shed a light on its efficacy in treatment of AMR.

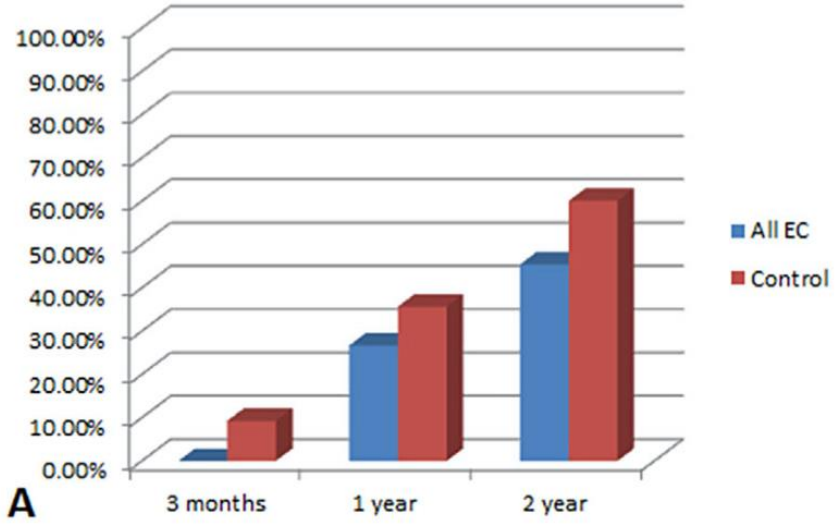




Subclinical ABMR in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	35.7% (10/28)	36.7% (11/30)	27.3% (6/22)
Control	46.2% (18/39)	36.8% (14/38)	15.1% (5/33)
p-value (EC vs. control)	P=0.46	P=1.0	P=0.32

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

American Journal of Transplantation 2015; 15: 1293–1302



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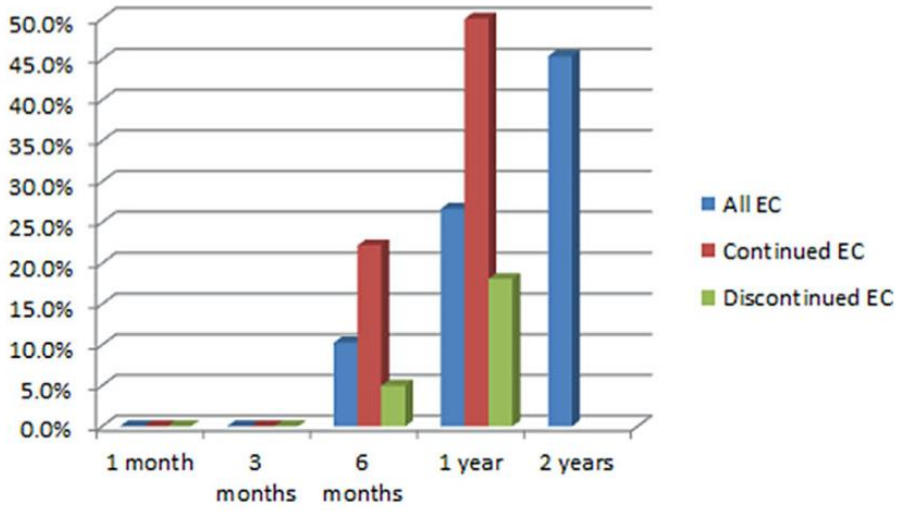
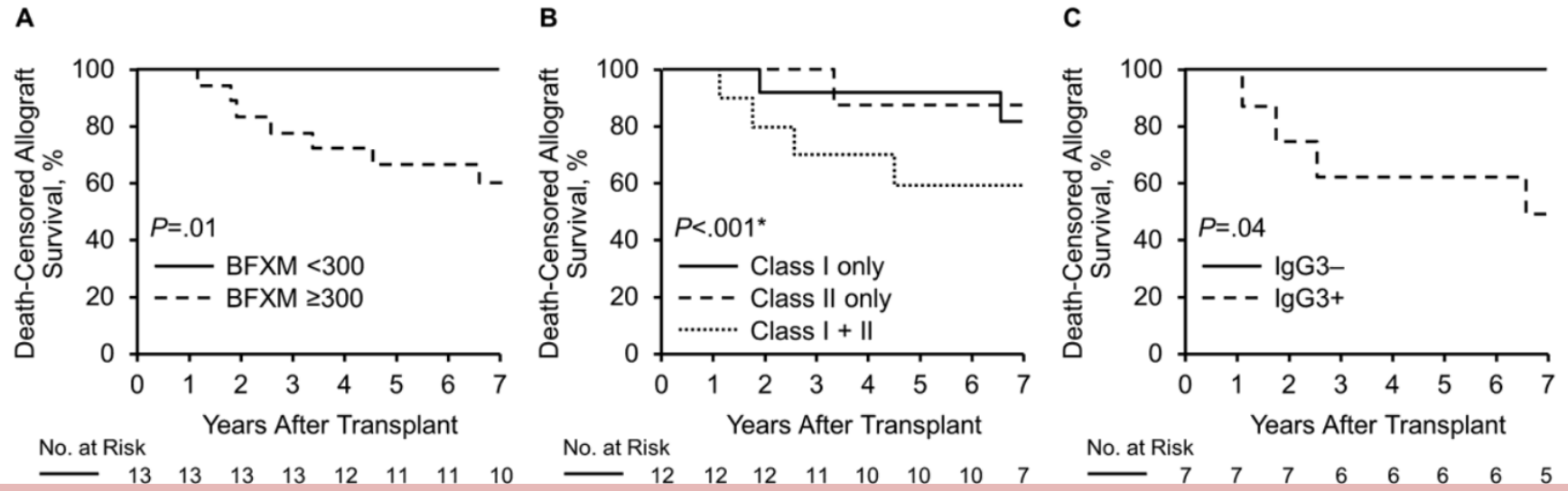


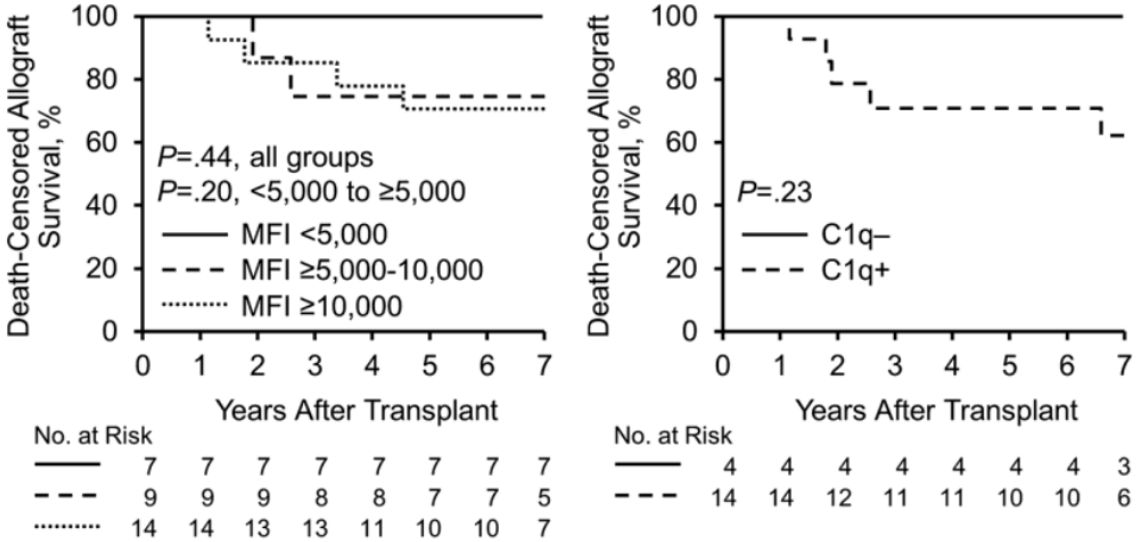
Transplant Glomerulopathy in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	0% (0/28)	26.7% (8/30)	45.4% (10/22)
Control	9.3% (4/43)	39.5% (15/38)	63.6% (21/33)
p-value (EC vs. control)	P=0.15	P=0.31	P=0.27

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

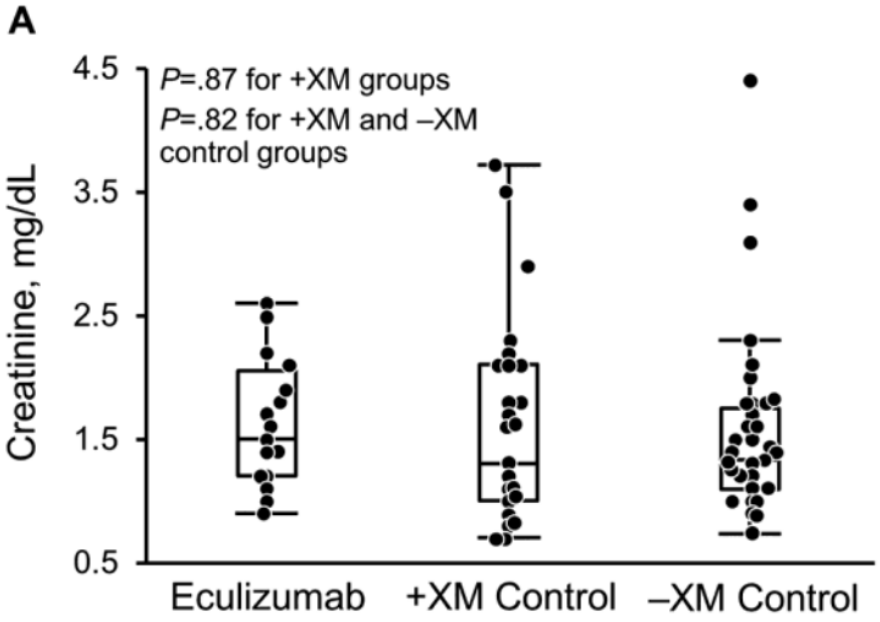
American Journal of Transplantation 2015; 15: 1293–1302

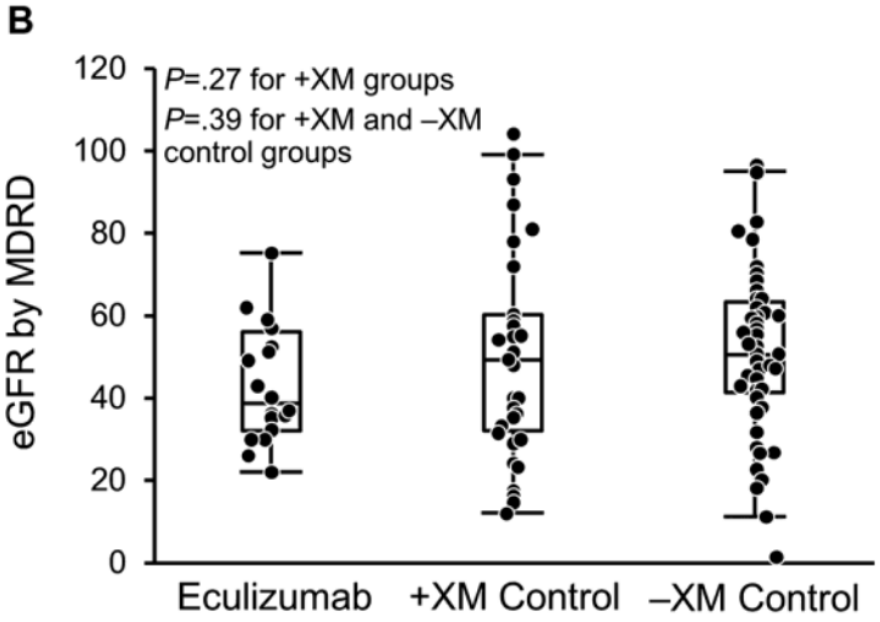


Baseline IgG3 positivity, BFXM ≥300 and class I+II DSA were associated with allograft loss. C1q positivity was also associated with allograft loss but did not reach statistical significance.

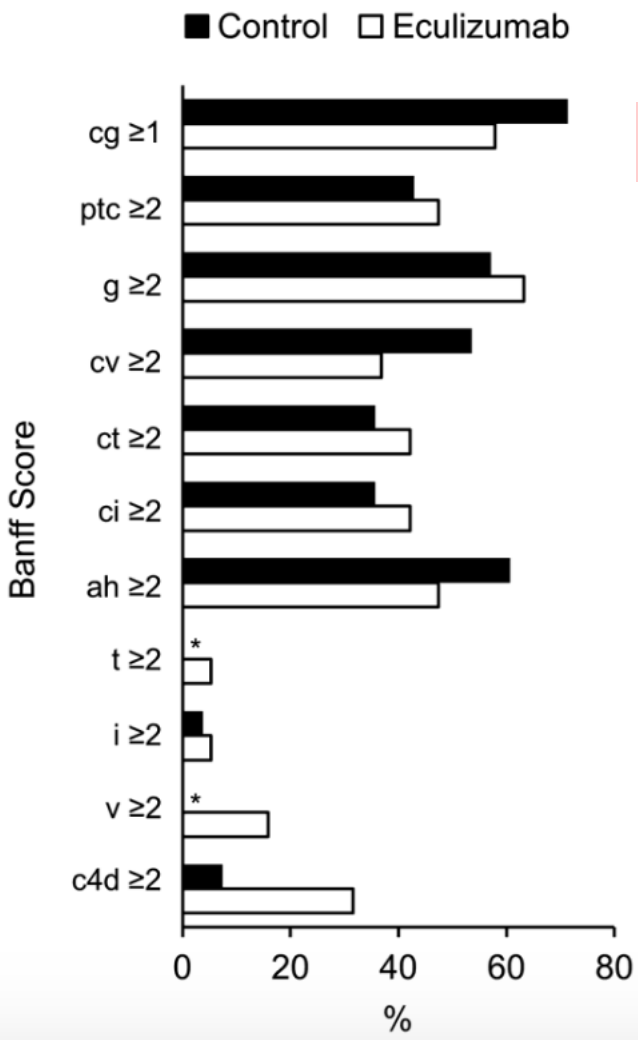


Am J Transplant. 2019 Jun;19(6):1671-1683



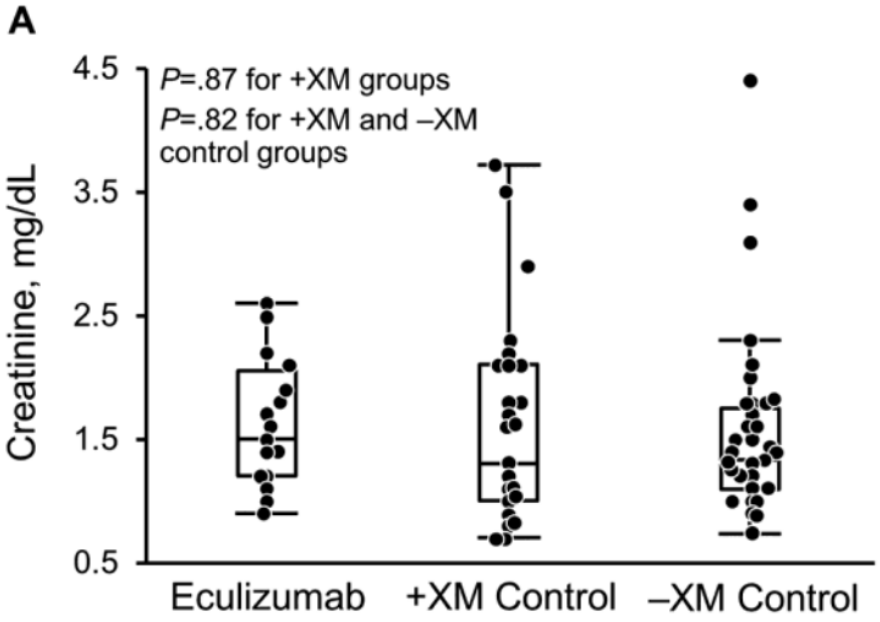


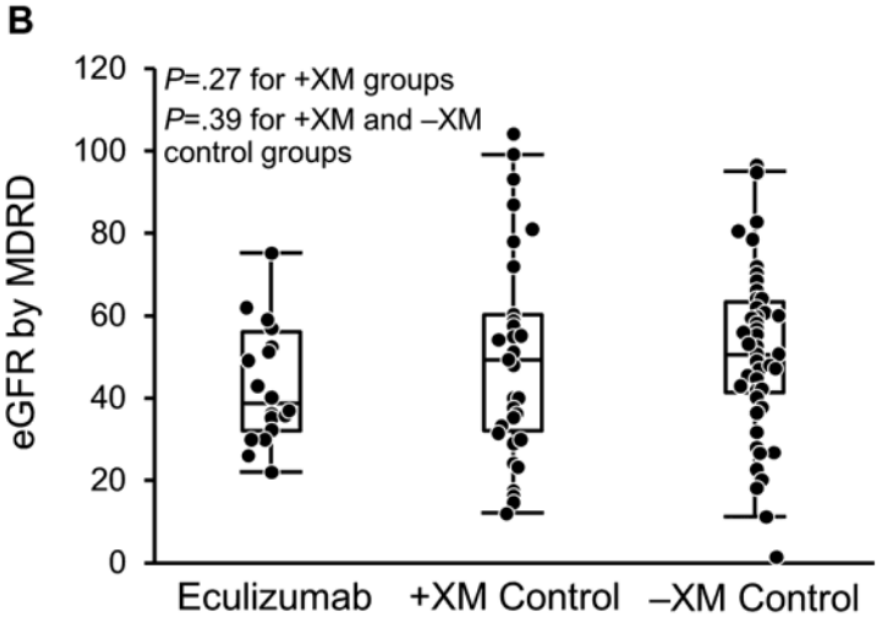
Am J Transplant. 2019 Jun;19(6):1671-1683



	Eculizumab +XM (%) (n=19)	Control +XM (%) (n=28)	*P Value*
Chronic ABMR cg score ≥0	57.9 (11)	71.4 (20)	.36
Peritubular capillaritis ptc score ≥2	47.4 (9)	42.9 (12)	.77
Glomerulitis g score ≥2	63.2 (12)	57.1 (16)	.77
Vascular intimal thickening cv score ≥2	36.8 (7)	53.6 (15)	.37
Tubular atrophy ct score ≥2	42.1 (8)	35.7 (10)	.76
Interstitial fibrosis ci score ≥2	42.1 (8)	35.7 (10)	.76
Arteriolar hyalinosis ah score ≥2	47.4 (9)	60.7 (17)	.39
Tubulitis t score ≥2	5.3 (1)	0.0 (0)	.40
Inflammation i score ≥2	5.3 (1)	3.7 (1)	1.0
Intimal arteritis v score ≥2	15.8 (3)	0.0 (0)	.06
C4d ≥2	31.6 (6)	7.4 (2)	.05

Am J Transplant. 2019 Jun;19(6):1671-1683





Am J Transplant. 2019 Jun;19(6):1671-1683

- Eculizumab-treated +XM patients had reduced allograft survival compared with −XM controls but similar survival to +XM controls.

- BFXM and complement- activating DSA (by IgG3 and C1q testing) may be used for risk stratification in +XM transplantation.

- C3a is a potent chemotactic molecule that may stimulate an inflammatory response in the allograft independent of the blockade of C5.
- Complement deposition (C4d+ staining) and complement binding DSA (C1q+), both relevant to activation of the proximal complement pathway, have been associated with chronic ABMR.

ISRCTN49958194 https://doi.org/10.1186/ISRCTN49958194

An investigation into the treatment of the donor kidney to see if this improves the recovery of the kidney after transplantation

Condition category
Injury, Occupational Diseases, Poisoning

Date applied
15/06/2012

Date assigned
03/08/2012

Last edited
21/05/2019

Prospective/Retrospective
Prospectively registered

Overall trial status
Completed

Recruitment status
No longer recruiting

Use of Eculizumab for Active Antibody-mediated Rejection That Occurs Early Post–kidney Transplantation

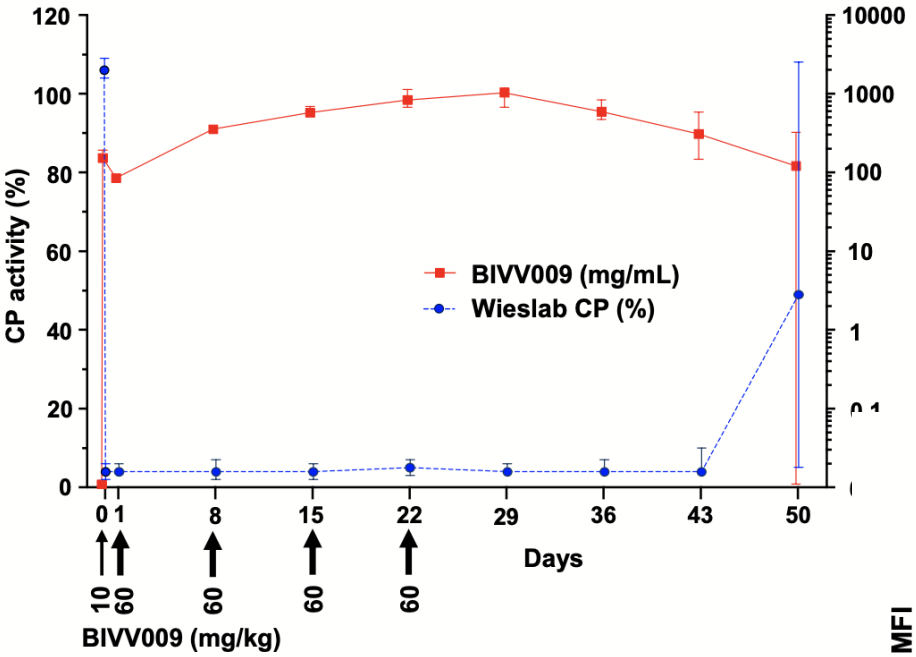
A Consecutive Series of 15 Cases

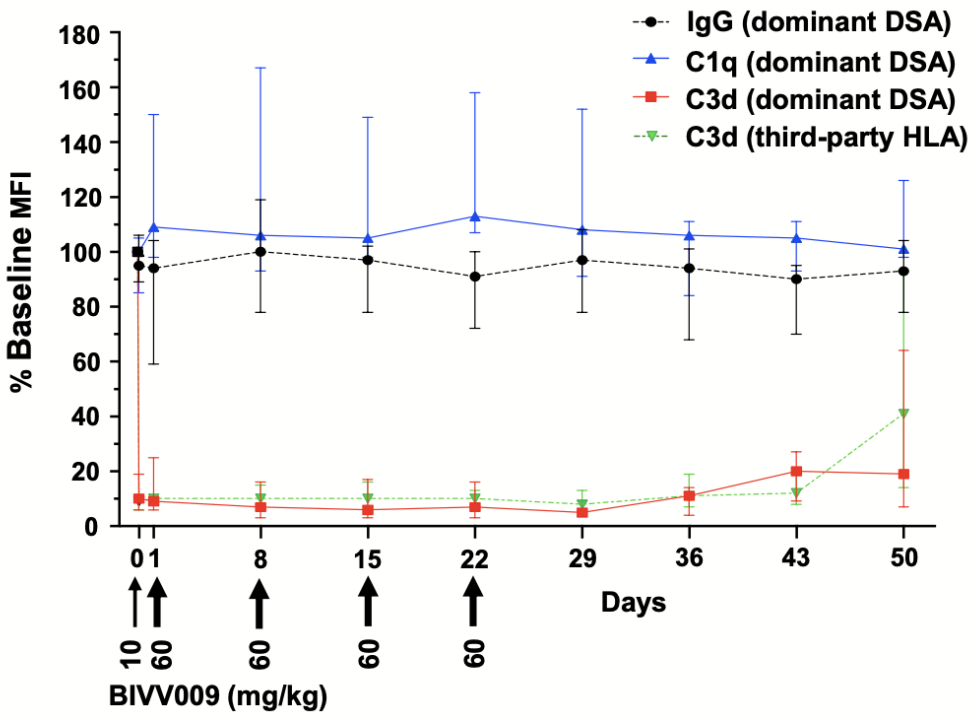
Tan, Ek Khoon MBBS[1]; Bentall, Andrew MD[2,3]; Dean, Patrick G. MD[1,3]; Shaheen, Mohammed F. MBBS[1]; Stegall, Mark D. MD[1,3]; Schinstock, Carrie A. MD[2,3]

Transplantation: November 2019 - Volume 103 - Issue 11 - p 2397–2404
doi: 10.1097/TP.0000000000002639

Conclusions. Prompt eculizumab treatment as primary therapy is safe and effective for early active AMR after kidney transplant or abrupt increases in donor-specific antibodies when biopsy cannot be performed for diagnosis confirmation.

Results. Fifteen patients had early active AMR at a median (interquartile range [IQR]) of 10 (7–11) days posttransplant and were treated with eculizumab ± plasmapheresis. Thirteen cases were biopsy proven, and 2 cases were presumed on the basis of donor-specific antibody trends and allograft function. Within 1 week of treatment, the median estimated glomerular filtration rate increased from 21 to 34 mL/min (P = 0.001); and persistent active AMR was only found in 16.7% (2/12) of biopsied patients within 4–6 months. No graft losses occurred, and at last follow-up (median [IQR] of 13 [12–19] mo), the median IQR estimated glomerular filtration rate increased to 52 (46–60) mL/min.


CP activity (%)
BIVV009 (μg/ml)
BIVV009 (mg/mL)
Wieslab CP (%)
Days
BIVV009 (mg/kg)
10
60
60
60
60


IgG (dominant DSA)
C1q (dominant DSA)
C3d (dominant DSA)
C3d (third-party HLA)
% Baseline MFI
Days
BIVV009 (mg/kg)
10
60
60
60
60