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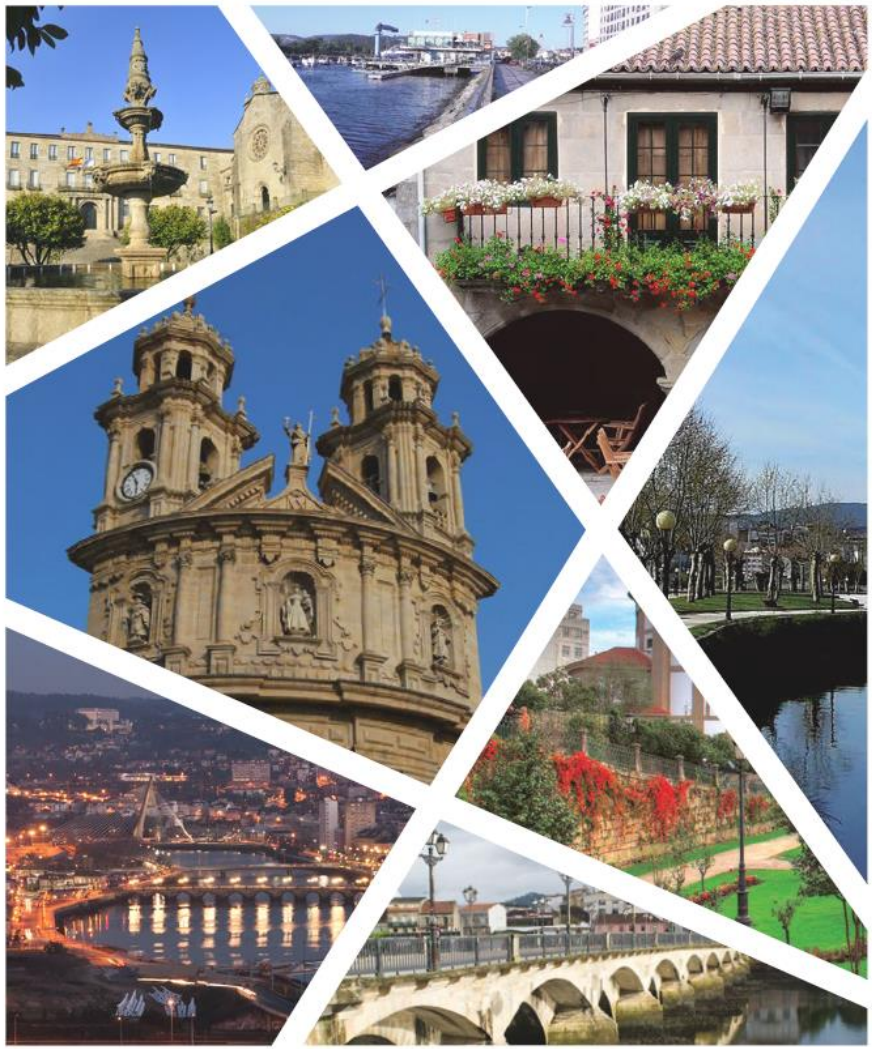
5º CONGRESO de la

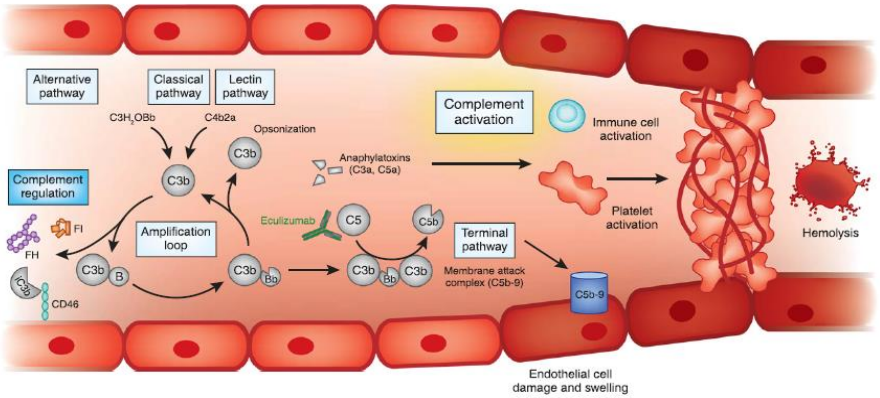
SOCIEDAD GALLEGA de NEFROLOGÍA

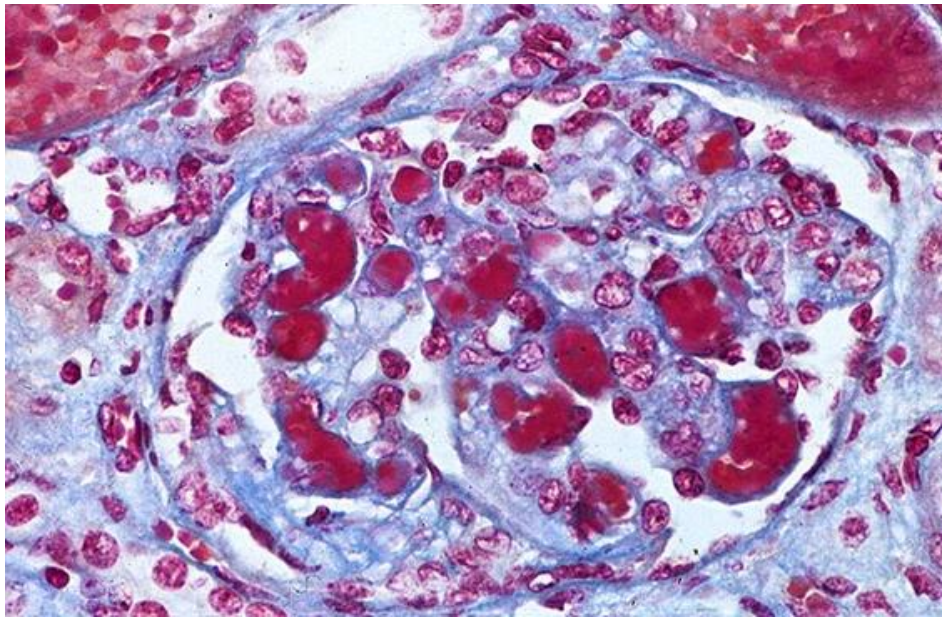
26 Y 27 DE OCTUBRE DE 2018

SEDE: **AFUNDACIÓN,** PONTEVEDRA

SGAN
sociedad gallega de nefrología

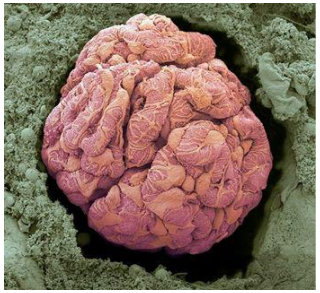






Enfermedades renales asociadas a la activación del complemento

Enrique Morales Ruiz. *Hospital Universitario 12 de Octubre Madrid*



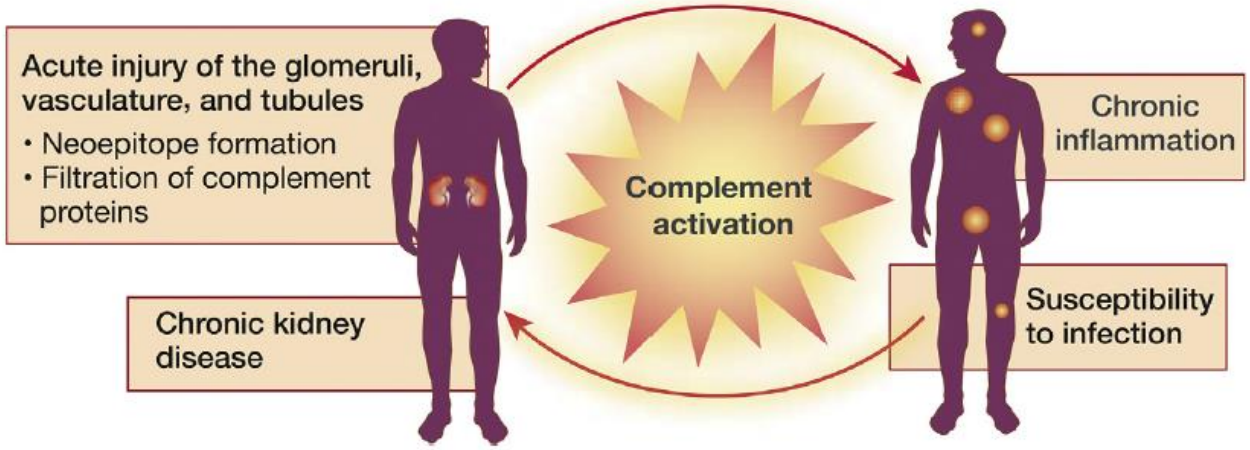


Table 1. Functions of the C cascade

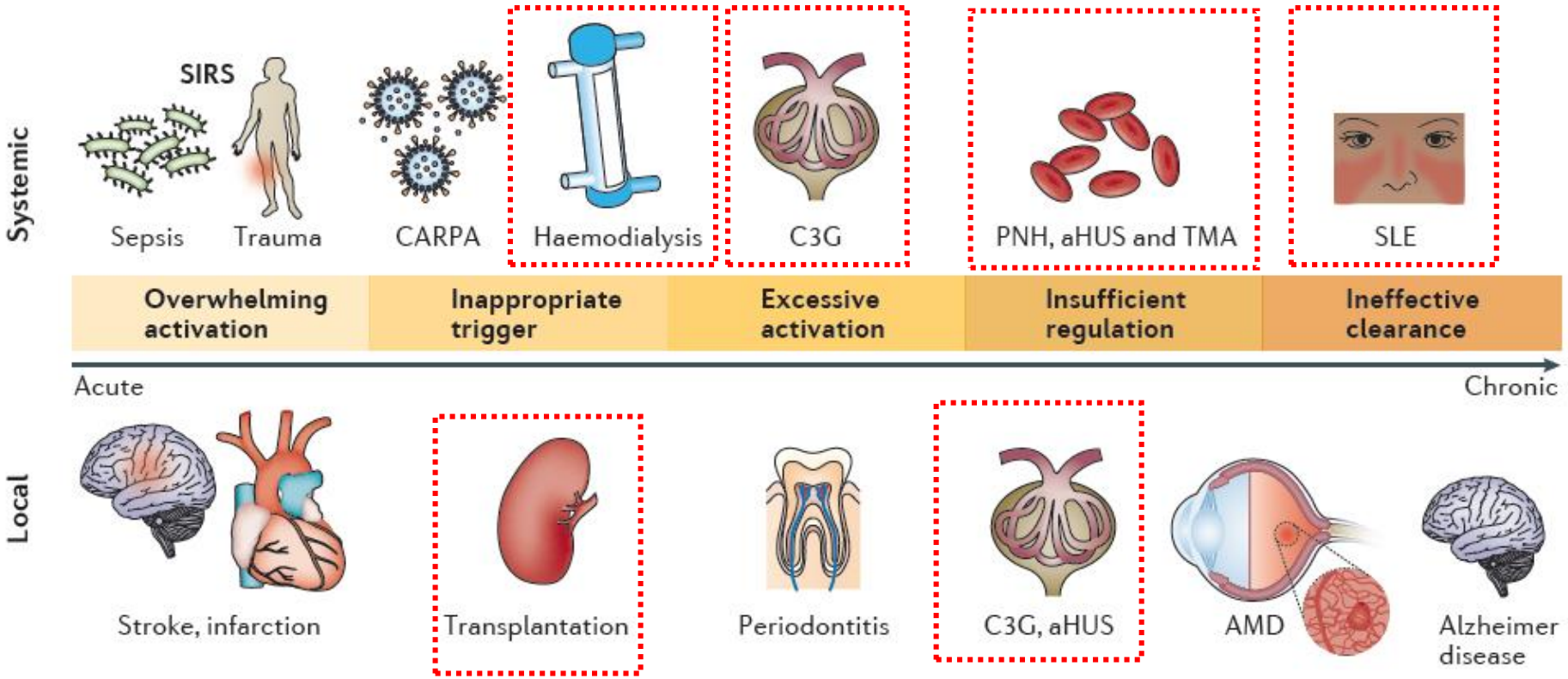
Adaptive Functions of C
- Opsonize target cells (pathogens and injured cells)
- Trigger vascular changes and inflammatory cell chemotaxis
- Lyse pathogens
- Provide costimulation and proliferation signals for immune cells
- Remove immune-complexes and cellular debris

Maladaptive Functions of C
- Promote tissue inflammation
- Directly cause injury to host cells
- Mediate cancer cell immune-evasion

Kidney International (2016)

The renaissance of complement therapeutics

Daniel Ricklin[1], Dimitrios C. Mastellos[2], Edimara S. Reis[3] and John D. Lambris[3]



Nat Rev Nephrol. 2018; 14(1):26-47

REVIEW

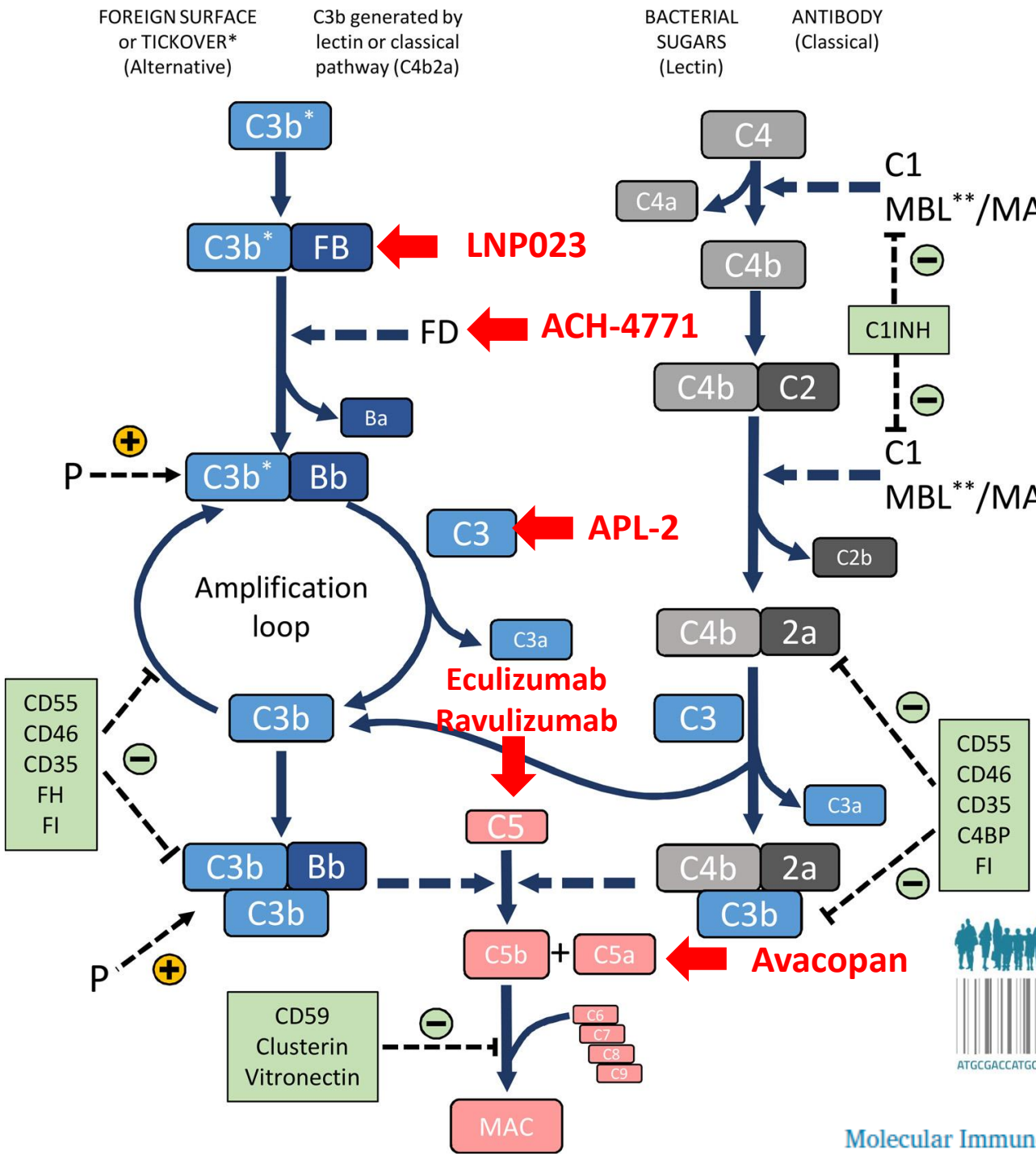
Complementopathies

Andrea C. Baines, Robert A. Brodsky *

- We will define complementopathy as a disorder in which:
  - In a number of diseases, **complement** plays a driving role in pathogenesis, whereas in others, complement is an ‘exacerbator’ of disease, inducing increased pathology initiated by a different disease trigger, thus driving inflammation and tissue damage
  - There is evidence that **inhibition of complement** disrupts or halts the pathogenic process of the disorder.

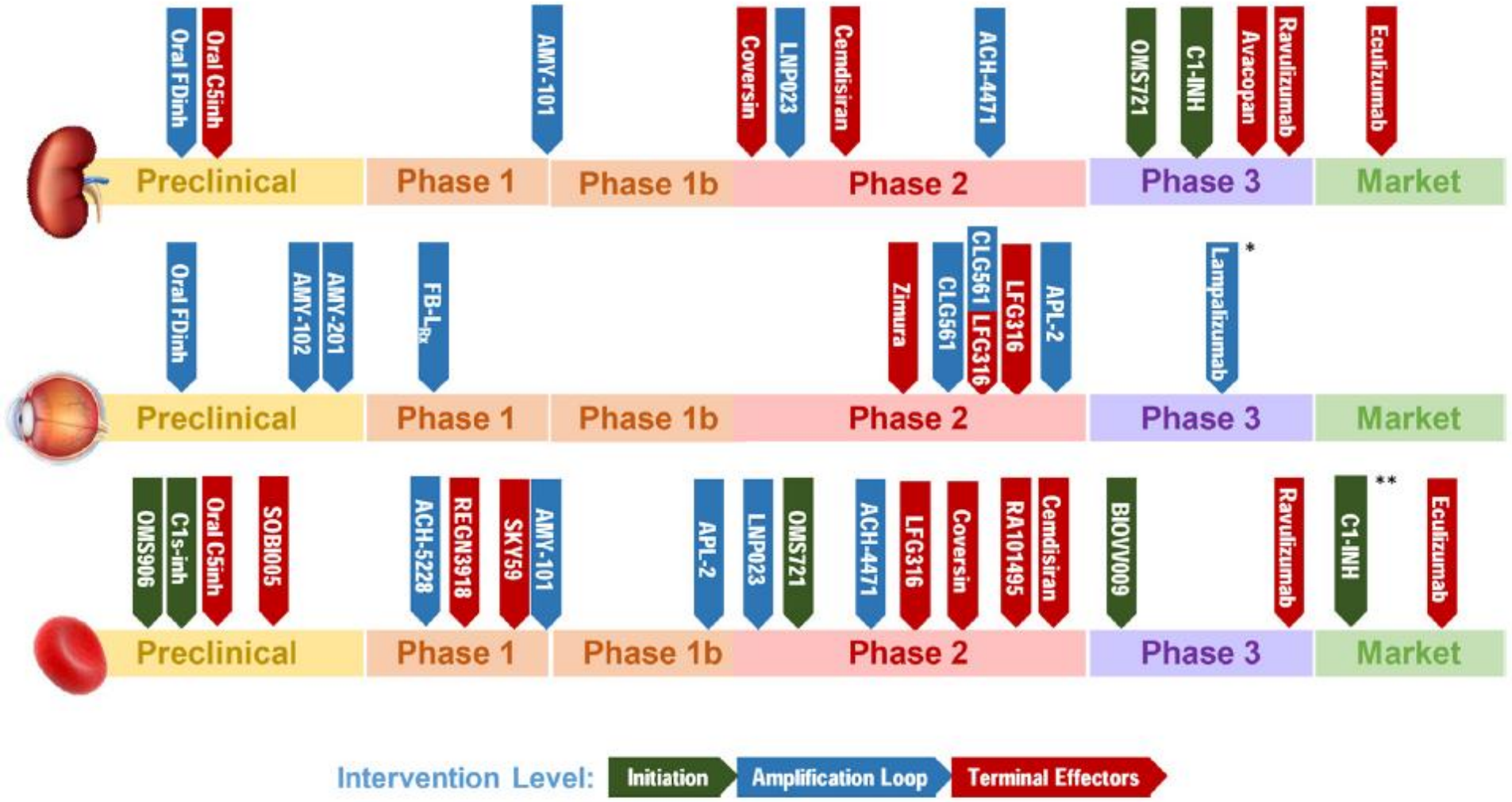
Blood Rev 2017;31(4):213-223

Developments in anti-complement therapy; from disease to clinical trial



GWAS

Molecular Immunology 102 (2018) 89–119

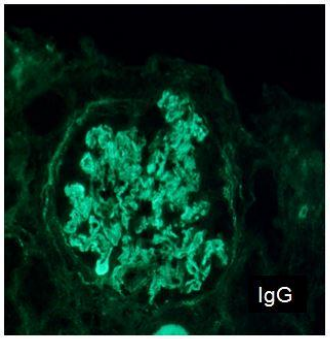

Oral FDinh
Oral C5inh
AMY-101
Coversin
LNP023
Cemdisiran
ACH-4471
OMS721
C1-INH
Avacopan
Ravulizumab
Eculizumab
Preclinical
Phase 1
Phase 1b
Phase 2
Phase 3
Market
Oral FDinh
AMY-102
AMY-201
FB-LRx
Zimura
CLG561
CLG561 LFG316
LFG316
APL-2
Lampalizumab
*
Preclinical
Phase 1
Phase 1b
Phase 2
Phase 3
Market
OMS906
C1s-inh
Oral C5inh
SOBI005
ACH-5228
REGN3918
SKY59
AMY-101
APL-2
LNP023
OMS721
ACH-4471
LFG316
Coversin
RA101495
Cemdisiran
BIOVV009
Ravulizumab
C1-INH
**
Eculizumab
Preclinical
Phase 1
Phase 1b
Phase 2
Phase 3
Market
Intervention Level:
Initiation
Amplification Loop
Terminal Effectors

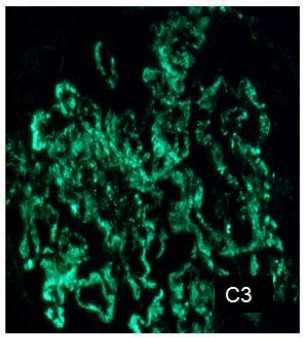

COMPLEMENT
THERAPHIES
'right drug to the right patient'

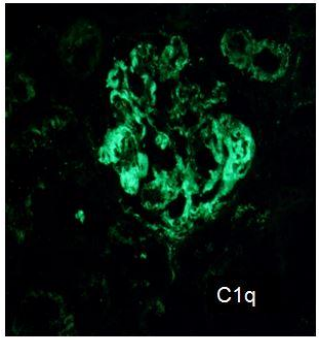
Evidence That the C System is Involved in Glomerular Diseases

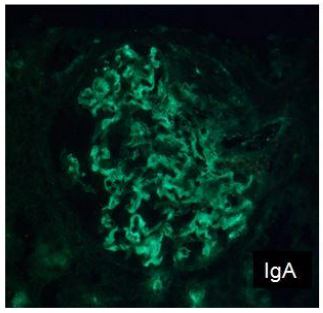
- As early as the 1960s it was understood that the C system was involved in antibody-mediated glomerular injury, (A Role of Polymorphonuclear Leukocytes and Complement in Nephrotoxic Nephritis. J Exp Med 122: 99–116, 1965)
- By the 1970s C proteins were detected in renal biopsy specimens from patients with GN, (Immunopathology and glomerulonephritis. Annu Rev Med 25: 83–98, 1974)
- Experimental evidence in both animal models and in patients links the C system with a large number of glomerular diseases.

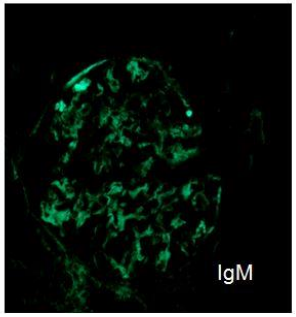
Joshua M. Thurman, and Carla M. Nester CJASN 2016;11:1856-1866


IgG

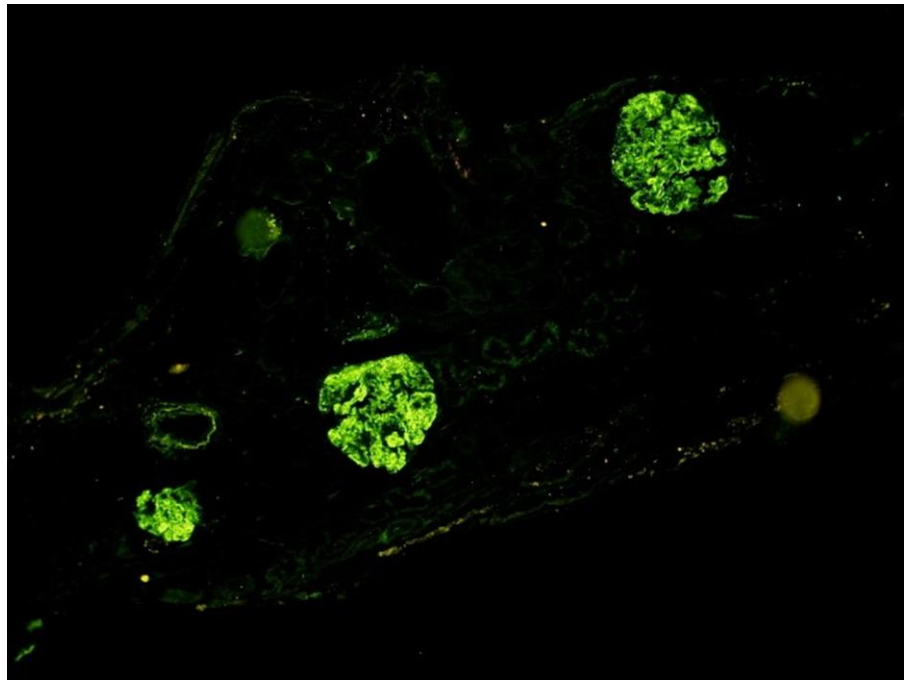

C3

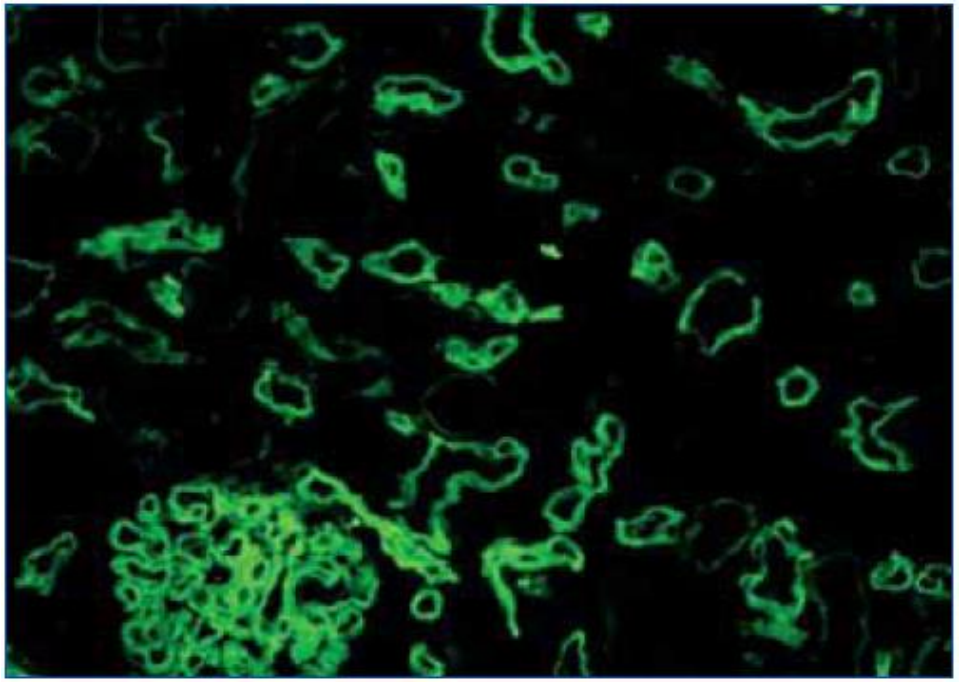

C1q

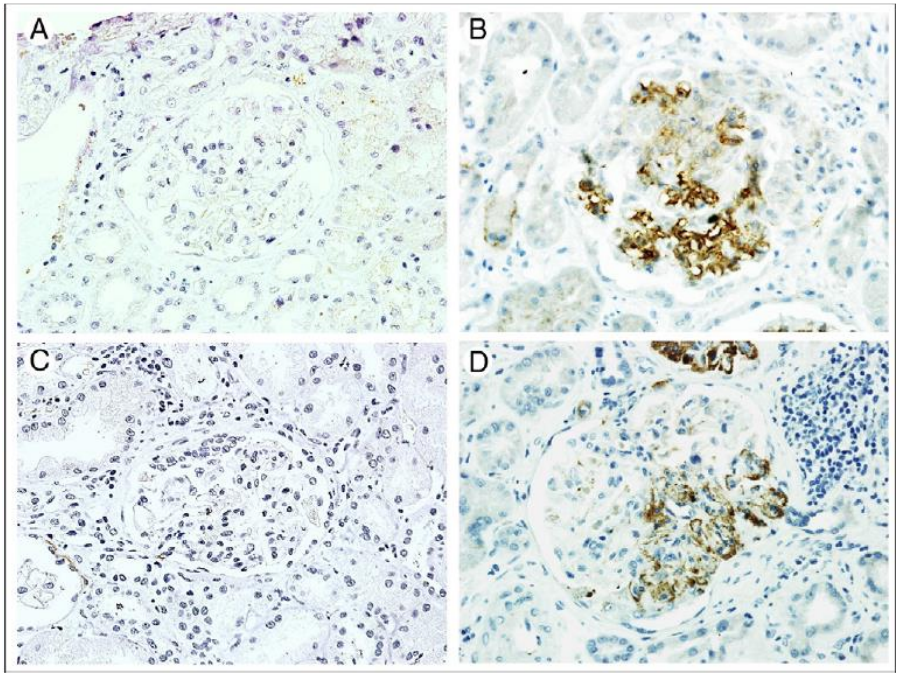

IgA


IgM


Cadenas kappa



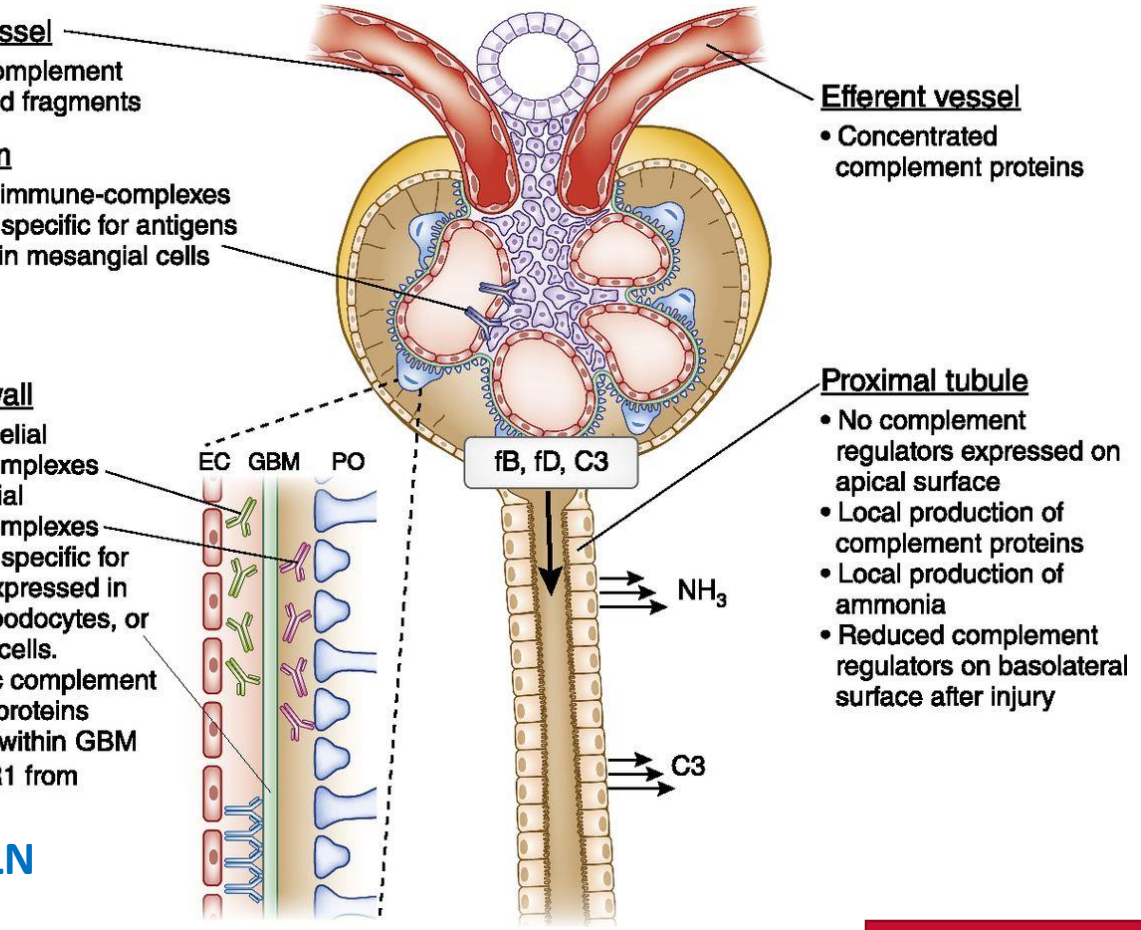



A
B
C
D

Mechanisms of C activation in glomerular diseases

Vasculature and glomerular endotelial cells (IgG, IgM, IC)

Tubulointerstitium (C3)



LN, MPGN

GBM (C3G)

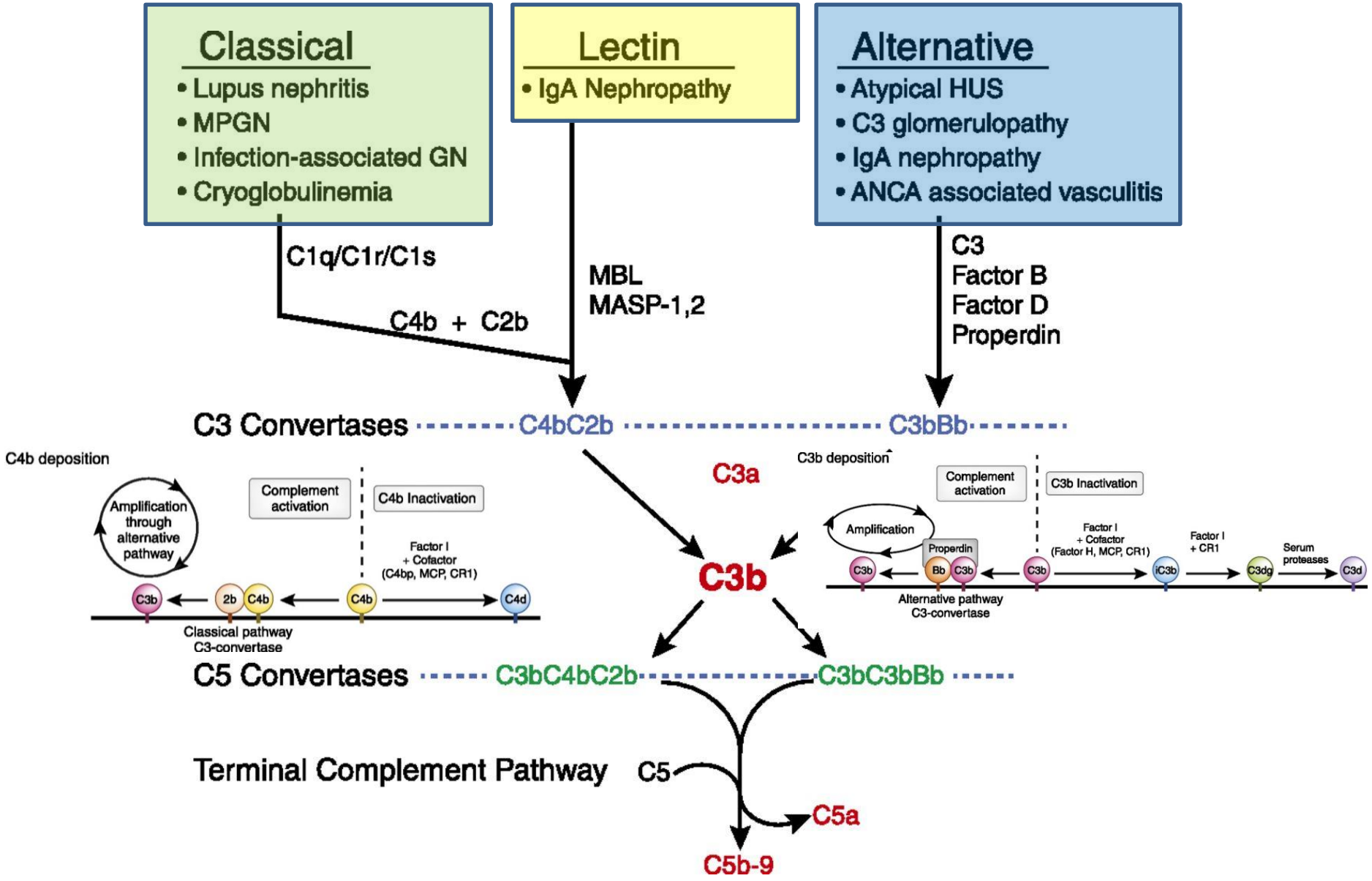
MGN, LN

Podocytes (CR1)

Mesangium (LN, GC3, IgAN)

Joshua M. Thurman, and Carla M. Nester CJASN 2016;11:1856-1866

Overview of the C cascade.



Joshua M. Thurman, and Carla M. Nester CJASN 2016;11:1856-1866

Table 2. Evidence that the C system is involved in glomerular diseases

Disease	C Protein Deposits[a]	Plasma Complement Protein Level	Autoantibodies to Complement Proteins	C Gene Variants Associated with Disease	Clinical Use of Complement Inhibitors
Atypical hemolytic uremic syndrome	C3 and C5b-9 deposits have been reported (94) C1q, C4d, C5b-9, MBL, and IgM reported in some cases (62)	↓C3 ↑C5a, ↑sC5b-9	Factor H	Factor H Factor I C3 Factor B CD46 CHFR1 CFHR3 CFHR5 Thrombomodulin	✓
C3 Glomerulopathy	Dominant C3 two orders of magnitude greater than that for Ig	↓C3, ↓factor B, ↓properdin, ↓C5, ↓C7 ↑Ba, ↑Bb, ↑C3d, ↑C5a, ↑sC5b-9	C3Nefs (>75%) C3b Factor H Factor B	Factor H Factor I C3 C8 Factor B CHFR1 CFHR2 CFHR3 CFHR5 CR1	✓
Lupus nephritis	C3, C4, C1q	↓C3, ↓C4, ↓C1q	C1q, C3	C1q, C1r/s, C2, C4	✓
Membranoproliferative GN	C3, C4, IgG, IgM	↓C3, ↓C4	C3Nefs	Factor H Factor I CD46	
Catastrophic antiphospholipid antibody syndrome		↓C3, ↓C4 ↑C3a, ↑C4a			✓
IgA nephropathy	C3, properdin, ±C4, ±MBL	↑C3a, ↑C3d		Factor H CFHR1 CFHR3	✓
ANCA associated vasculitis	C3 and Ig can be seen (95)	↑C3a, ↑C5a, ↑sC5b-9, ↑Bb			✓
Postinfectious GN	C3, ±C4	↓C3, ↓C5, ↓properdin			
Tubulointerstitial diseases	C3 on brush border	Urine iC3b, Bb, C5b-9			

Síndrome urémico-hemolítico del adulto

J. Montoliu, A. Darnell, A. Torras, A. Botey y L. Revert

Incidencia

Seis pacientes: 2 varones
4 mujeres
Edad media: 36 años (20-52)

	N.º casos	N.º total casos
Etiología		
Idiopático	3	6
Anovulatorios	2	6
Embarazo complicado	1	6
Manifestaciones clínicas		
Insuficiencia Renal (Cr > 5 mg/100 cc)	6	6
Anemia hemolítica microangiopática	6	6
Trombocitopenia (150.000/mm³)	6	6
Hipertensión grave (TA diastólica > 120 mmHg)	6	6
Oliguria (Diuresis < 500 cc/24 horas)	4	6
Insuficiencia cardiaca	3	6
Hiperreninemia	4	4
Aumento PDF	2	6
Hipocomplementemia	1	6
Alteraciones de la coagulación	0	6
Sintomatología neurológica	0	6
Evolución		
Exitus	1	6
IRC terminal en hemodiálisis periódica	3	6
Recuperación parcial de la función renal (IRC)	2	6
Complicaciones durante la fase aguda		
Pericarditis	2	6
Septicemia	2	6
Pancreatitis	2	6

mm³ respectivamente). La hipertensión fue la forma de presentación más frecuente en nuestra serie, ya que cuatro enfermos ingresaron en el Hospital con motivo de una crisis hipertensiva. La retinopatía hipertensiva, según la clasificación de Keith y Wagener era de grado IV en tres casos, de grado III en dos y de grado II en uno. La hiperten-

Inmunofluorescencia. En tres casos fue evidente la presencia de C3 en forma de nódulos segmentarios y focales en los capilares glomerulares. En otra biopsia la presencia de C3 se detectó únicamente en los vasos y no en el glomérulo. Sólo en un caso se detectaron cantidades variables de C1q, C4 e

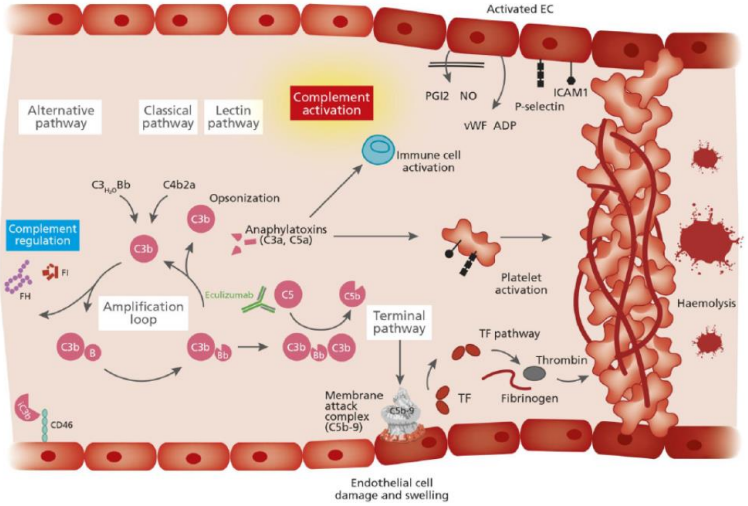
Formas etiológicas del SUH del adulto

1. Idiopático [3,31]
2. Anticonceptivos orales [23]
3. Posparto [24-26]
4. Complicaciones del embarazo [3,27-30]
5. Asociado a infecciones [3,16-19]
6. Formas familiares [20,21]
7. Formas recurrentes [22]
8. Formas hipocomplementémicas [34-36]

Tratamiento. Todos los casos fueron tratados con hipotensores. Cuatro de los seis enfermos precisaron hemodiálisis. Unicamente una paciente recibió tratamiento anticoagulante y fibrinolítico con heparina y estreptocinasa durante dos semanas. Se interrumpió el tratamiento con motivo de un episodio de hemorragia gastrointestinal. Esta misma paciente fue binefrectomizada.

Med. clín. (Barcelona), 74: 5, 1980

Atypical hemolytic uremic syndrome and C3 glomerulopathy: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

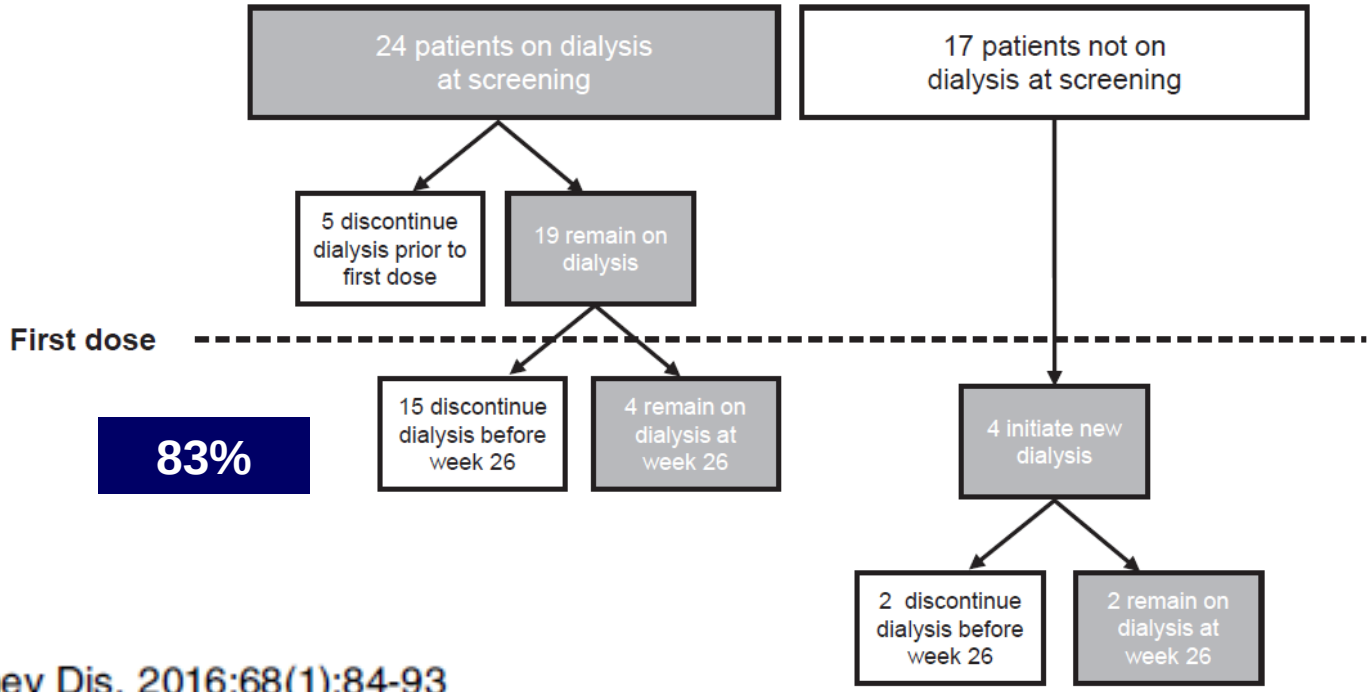


Molecular Immunology 102 (2018) 89–119

Kidney Int. 2017; 91(3):539-551

Table 2. TMA, Hematologic, and Kidney Disease Outcomes for Eculizumab in Adult Patients With aHUS, by 26 Weeks of Treatment

Primary and Secondary End Points	ITT Population (N = 41)	Dialysis[a] (n = 24)	No Dialysis[a] (n = 17)
Primary end point			
Complete TMA response[b]	30 (73%)	17 (71%)	13 (77%)
95% CI	57%-86%	49%-87%	50%-93%
TMA outcomes			
Modified complete TMA response[b]	23 (56%)	15 (63%)	8 (47%)
95% CI	40%-72%	41%-81%	23%-72%
TMA event-free status[b]	37 (90%)	22 (92%)	15 (88%)
95% CI	77%-97%	73%-99%	64%-99%
Hematologic outcomes			
Platelet count normalization[b]	40 (98%)	23 (96%)	17 (100%)
95% CI	87%-100%	79%-100%	81%-100%
Change from baseline in platelet count, $\times 10^3/\mu L$ (n = 27)[c]	135 ± 114	163 ± 120	87 ± 88
	$P < 0.001$	$P < 0.001$	$P = 0.01$
LDH normalization[b]	37 (90%)	23 (96%)	14 (82%)
95% CI	77%-97%	79%-100%	57%-96%
Hematologic normalization[b]	36 (88%)	22 (92%)	14 (82%)
95% CI	74%-96%	73%-99%	57%-96%

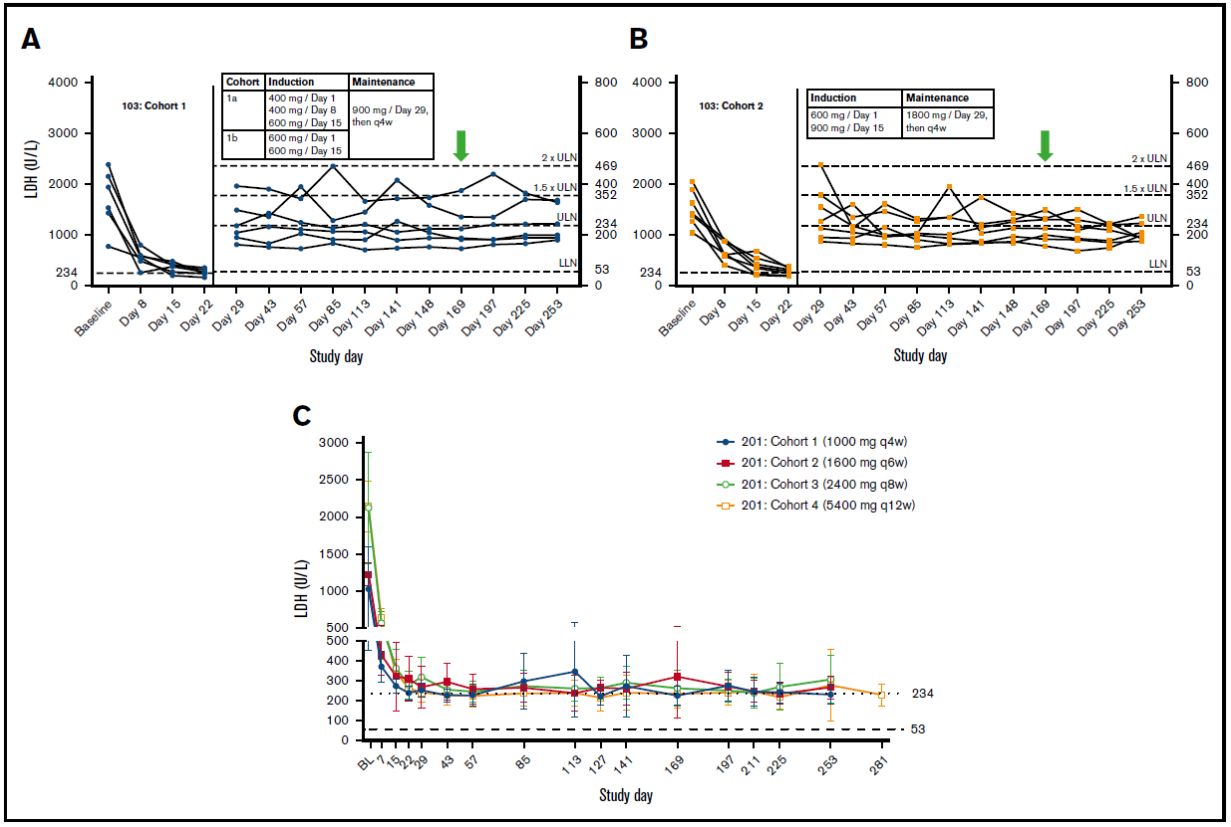


Am J Kidney Dis. 2016;68(1):84-93

Design and preclinical characterization of ALXN1210: A novel anti-C5 antibody with extended duration of action

Ravulizumab

Ravulizumab (ALXN1210) in patients with paroxysmal nocturnal hemoglobinuria: results of 2 phase 1b/2 studies

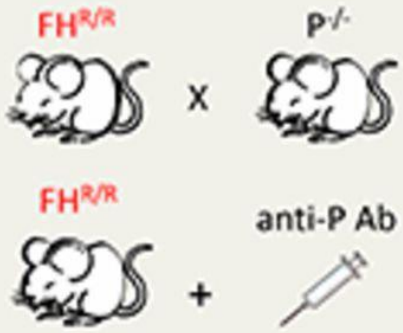


Blood Adv. 2018 Sep 11; 2(17): 2176–2185.

Blocking properdin prevents complement-mediated hemolytic uremic syndrome and systemic thrombophilia in mice

METHODS

Blocking of P function by genetic deletion or mAb inhibition in a murine model of aHUS ($FH^{R/R}$)

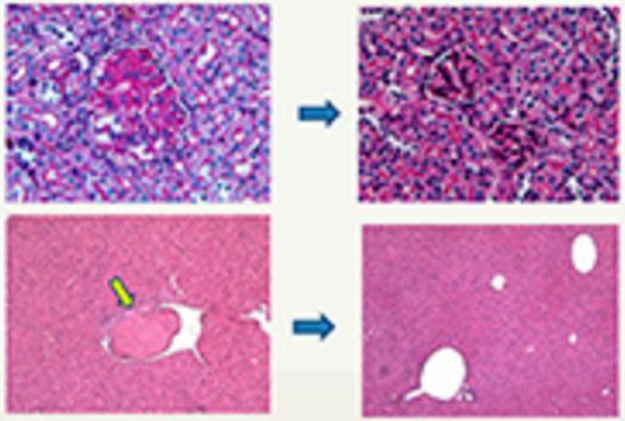


$FH^{R/R}$: W1206R mutation in complement factor H

P: properdin, a positive regulator of the alternative pathway of complement activation

OUTCOME

P deficiency or anti-P mAb treatment rescued $FH^{R/R}$ mice from lethal aHUS and systemic thrombophilia



CONCLUSION

Properdin contributed critically to aHUS pathogenesis and its inhibition in this disease should have beneficial effect and be therapeutic.

doi: 10.1681/ASN.2017121244

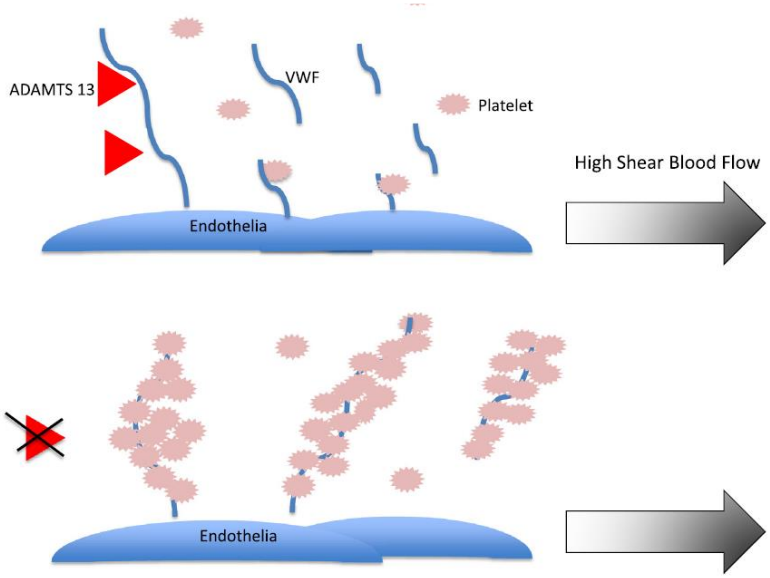
JASN

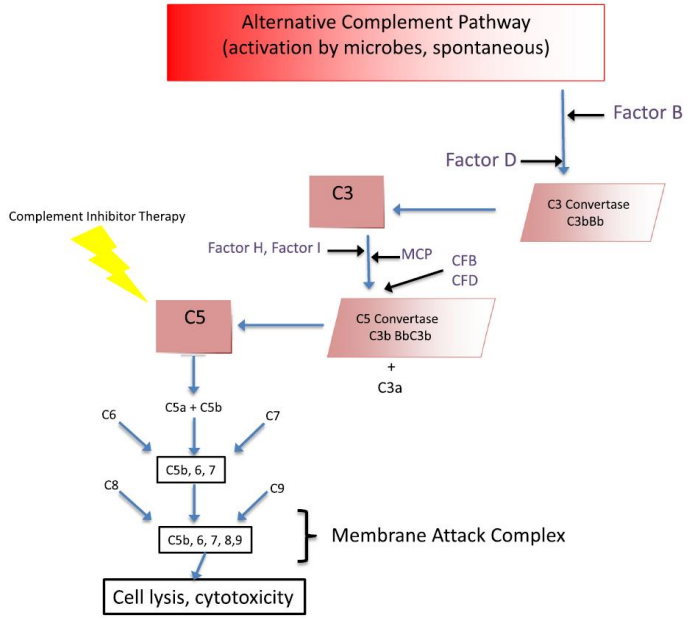
Microangiopathic Hemolytic Anemia in Pregnancy

Lucy Neave [a], Marie Scully [b,*]

Causes of pregnancy-associated TMA

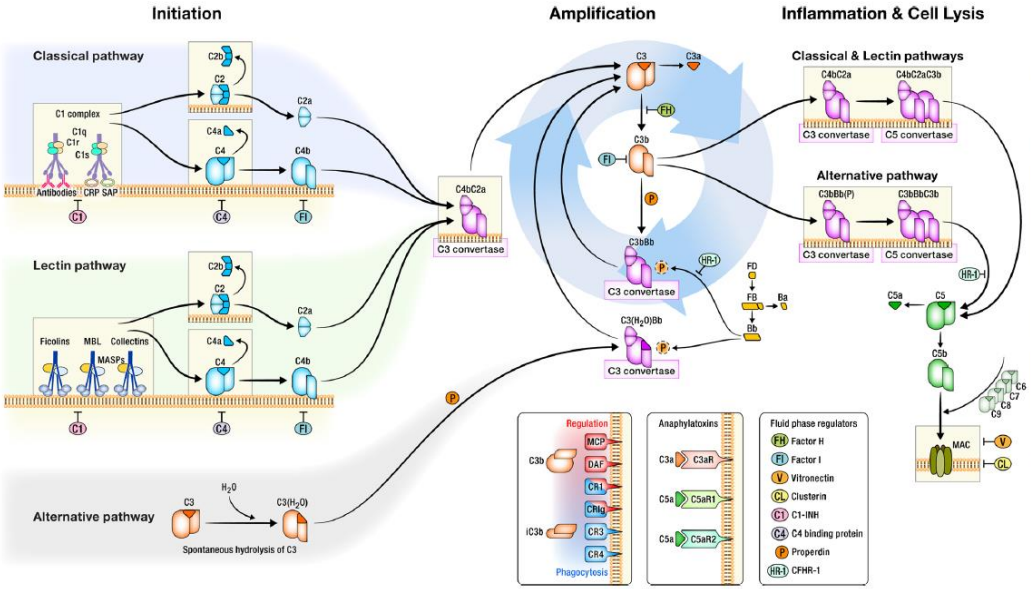
Pregnancy-associated TMA	TMA presenting in pregnancy
Hypertension of pregnancy	Lupus nephritis/SLE
Preeclampsia	Vasculitis
	APLS
HELLP syndrome	Sepsis
AFLP	Severe hemorrhage
Placental abruption	TTP
Undefined TMA	CM HUS

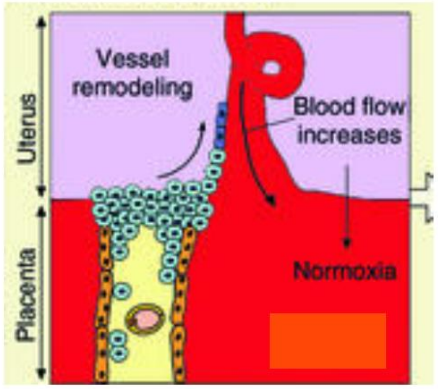




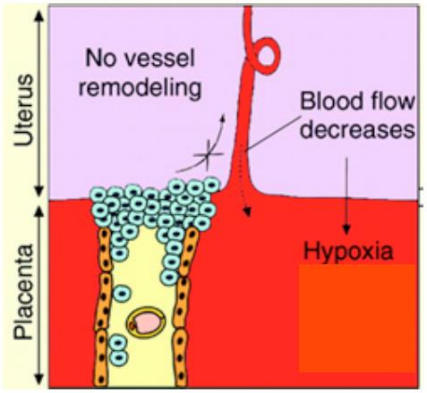
The Complement Alternative Pathway and Preeclampsia

Layan Alrahmani [1] · Maria Alice V. Willrich [2]





Healthy Pregnancy



Preeclampsia

Mutations in Complement Regulatory Proteins Predispose to Preeclampsia: A Genetic Analysis of the PROMISSE Cohort

PLoS Medicine March 2011 | Volume 8 | Issue 3 | e1001013

Jane E. Salmon[1]*, Cara Heuser[2], Michael Triebwasser[3], M. Kathryn Liszewski[3], David Kavanagh[4], Lubka Roumenina[5], D. Ware Branch[2], Tim Goodship[4], Veronique Fremeaux-Bacchi[5], John P. Atkinson[3]

PROMISSE, a prospective study of 250 pregnant patients with SLE and/or APL Ab

40 patients who had preeclampsia and found heterozygous mutations in seven (18%)

Current Hypertension Reports (2018) 20:40

Factor H, membrane cofactor protein, and factor I mutations in patients with hemolysis, elevated liver enzymes, and low platelet count syndrome

Fadi Fakhouri,[1] Mathieu Jablonski,[1] Jacques Lepercq,[2] Jacques Blouin,[3] Alexandra Benachi,[4] Maryvonne Hourmant,[5] Yves Pirson,[6] Antoine Dürrbach,[7] Jean-Pierre Grünfeld,[1] Bertrand Knebelmann,[1] and Véronique Frémeaux-Bacchi[3,8]

Table 2. Plasma complement component level and molecular genetic abnormalities found in 11 patients with HELLP syndrome

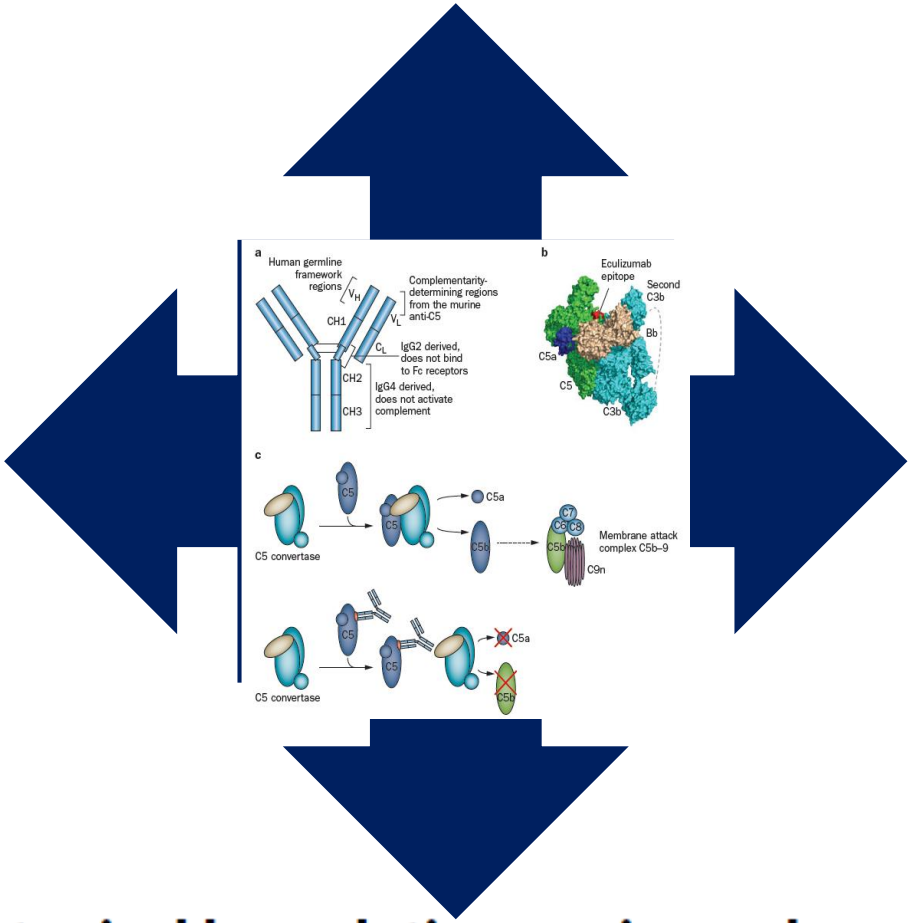
Patient	C3, mg/L	C4, mg/L	CFB, mg/L	CFH, mg/L	CFI, mg/L	MCP, MFI	Genetics abnormality	Mutations	Mutation characteristics
1	829	304	144	719	88	nd	*CFH*	pArg303Gln	Located in the SCR-1/5 fragment of *FH*, which is important for cofactor, C3b-binding, and decay-accelerating activity
2	1020	232	135	657	75	791	*CFI*	pArg345Gln (c1034G>A)	Located near the previously reported mutation I322T; functional analysis revealed a marked defect in both C3b and C4b cofactor activity[10]
3	899	217	127	540	70	359	*CFI*	pHist183Arg (c548A>G)	Located in the heavy chain domain that is important for C3b binding and the restriction of *CFI*[10]
4	912	199	125	652	77	966	*MCP*	pAla304Val	A304V mutation leads to deficiency in MCP to control the alternative pathway of complement activation on a cell surface[11]
5	**664**	169	**85**	555	54	1096			
6	**639**	109	**82**	474	58	894			
7	976	245	**75**	836	99	906			
8	1150	254	151	714	60	nd			
9	779	231	125	591	67	968			
10	1170	354	150	759	72	985			
11	1150	314	156	708	84	1246			
Normal values	660-1250	93-320	90-320	338-682	42-78	600-1500			

Eculizumab in pregnancy: a narrative overview

Laura Sarno[1] · Antonella Tufano[2] · Giuseppe Maria Maruotti[1] · Pasquale Martinelli[1] · Mario M. Balletta[3] · Domenico Russo[3]

Eculizumab: passage across the human placenta and in breast milk

Paroxysmal nocturnal hemoglobinuria and eculizumab treatment in pregnancy



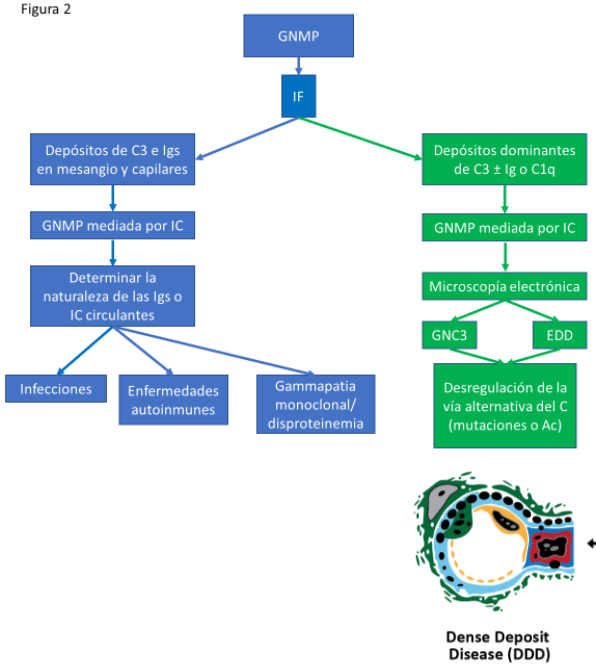
HELLP syndrome and eculizumab treatment

Atypical hemolytic uremic syndrome and eculizumab treatment in pregnancy

J Nephrol. 2018 Aug 29

The Role of Complement in C3 Glomerulopathy (C3G)

Figura 2



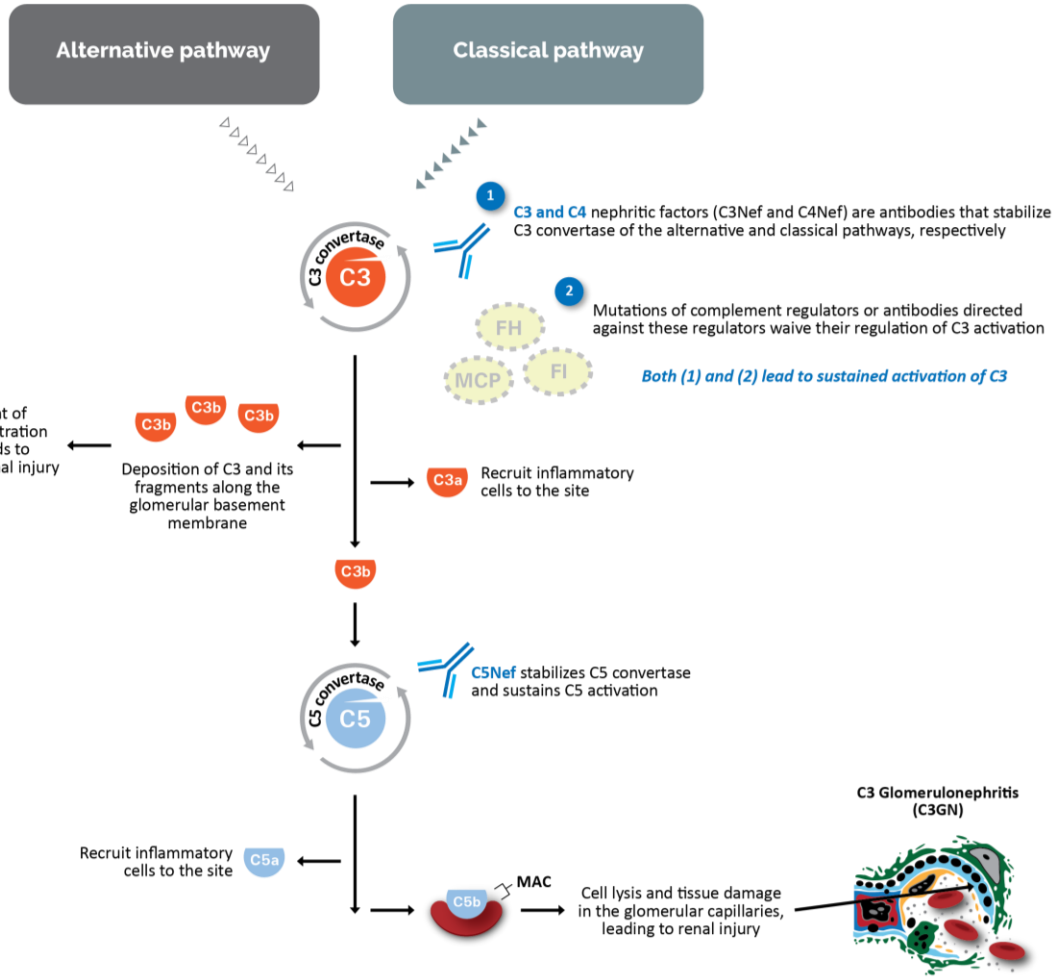


Table 2| Morphological features of C3G

Light microscopy

Active lesions

- Mesangial expansion with or without hypercellularity
- Endocapillary hypercellularity including monocytes and/or neutrophils
- Capillary wall thickening with double contours (the combination of capillary wall thickening and mesangial increase is referred to as a membranoproliferative pattern)
- Necrosis
- Cellular/fibrocellular crescents

Chronic lesions

- Segmental or global glomerulosclerosis
- Fibrous crescents

Immunofluorescence microscopy

- Typically dominant C3 staining

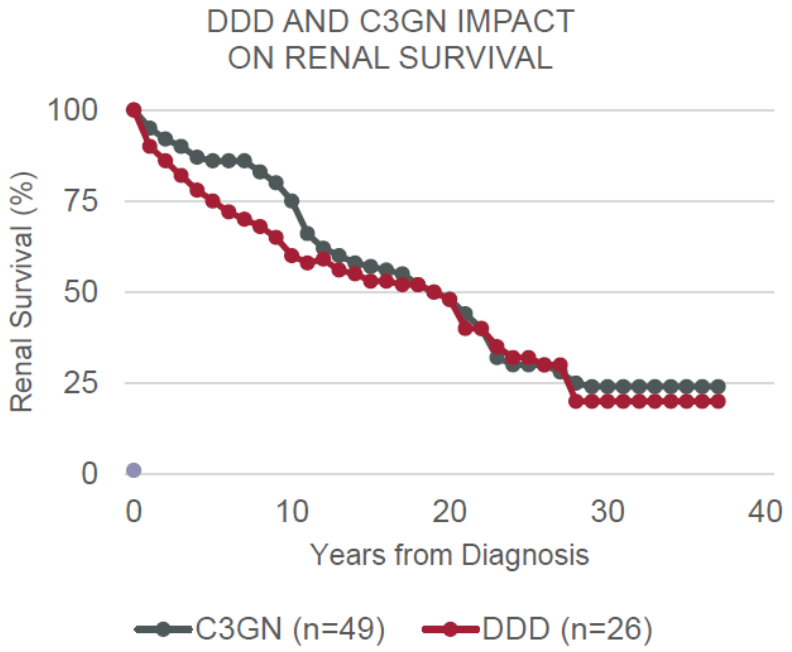
Electron microscopy

- DDD: Dense osmiophilic mesangial and intramembranous electron dense deposits
- C3GN: Amorphous mesangial with or without capillary wall deposits including subendothelial, intramembranous and subepithelial electron dense deposits
- Subepithelial "humps" may be seen in both DDD and C3GN

Kidney International (2017) **91,** 539–551

C3 Glomerulopathy (C3G)

- C3G
  - Dense deposit disease (DDD)
  - C3 glomerulonephritis (C3GN)
- Estimated prevalence of 8–12 people affected per million in major markets
  - Incidence rate of 1–2 per million patients diagnosed with C3G on an annual basis
- There are no approved treatments indicated for patients with C3G
  - Non-specific treatment approaches include blood pressure control and broad immunosuppression

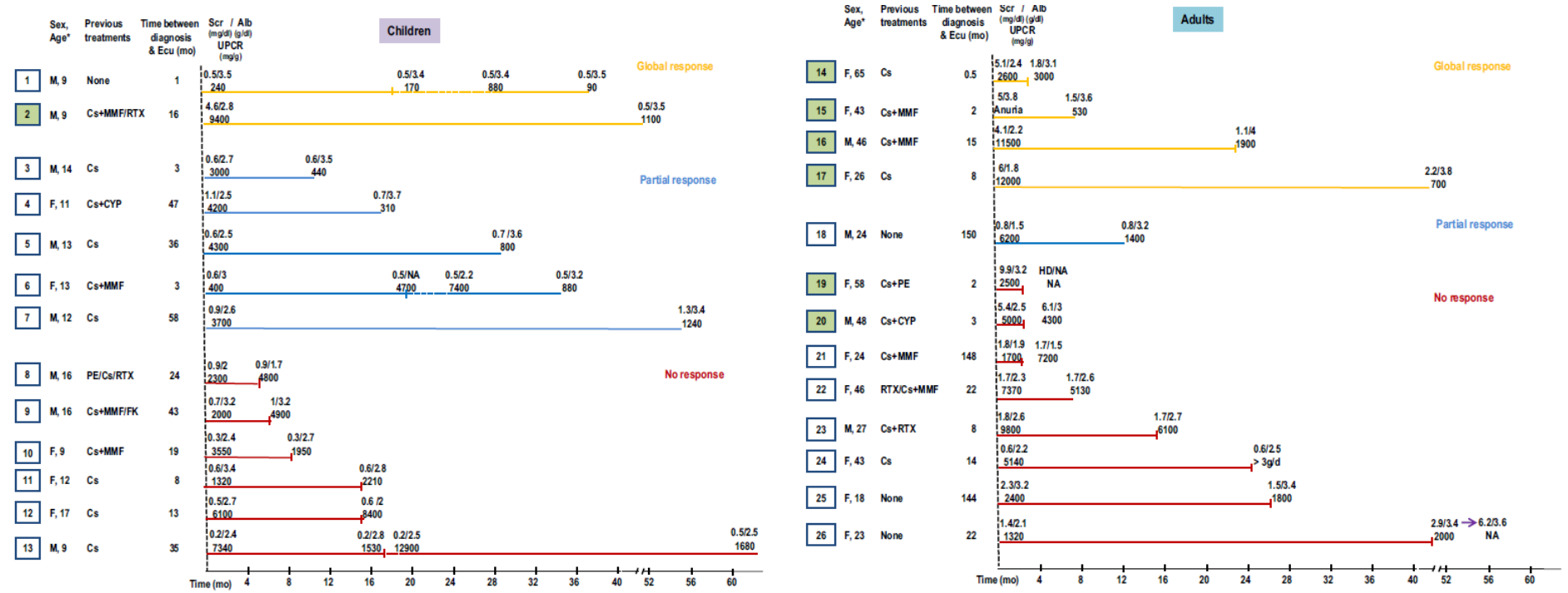


Barbour et al. (2015); NICE C3G Evidence Summary (2015).

Sources: Servais et al (2013); Medjeral-Thomas et al (2014); Data on File. Achillion Pharmaceuticals. 2016.

Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerulopathy

Moglie Le Quintrec, Anne-Laure Lapeyraque, Arnaud Lionet, Anne-Laure Sellier-Leclerc, Yahsou Delmas, Véronique Baudouin, Eric Daugas, Stéphane Decramer, Leila Tricot, Mathilde Cailliez, Philippe Dubot, Aude Servais, Catherine Mourey-Epron, Franck Pourcine, Chantal Loirat, Véronique Frémeaux-Bacchi, and Fadi Fakhouri



Results: 26 patients (13 children/adolescents) were included. 22 (85%) patients had received steroids, plasma exchange, or immunosuppressive therapy before eculizumab, and 3 of them had rapid progression of their kidney disease despite treatment. At the initiation of eculizumab therapy, 11 (42%) patients had chronic kidney disease, 7 (27%) had rapidly progressive disease, and 3 (12%) required dialysis. After eculizumab treatment (median duration, 14 months), 6 (23%) patients had a global clinical response; 6 (23%), a partial clinical response; and 14 (54%), no response.

Am J Kidney Dis. 2018 Feb 8

ChemoCentryx Reports Improvement in Renal Physiology and Stabilization of Kidney Function Following Treatment with Orally Administered Complement Inhibitor CCX168 (Avacopan) in Patient with Refractory C3 Glomerulopathy

Controlled Trial Evaluating Avacopan in C3 Glomerulopathy

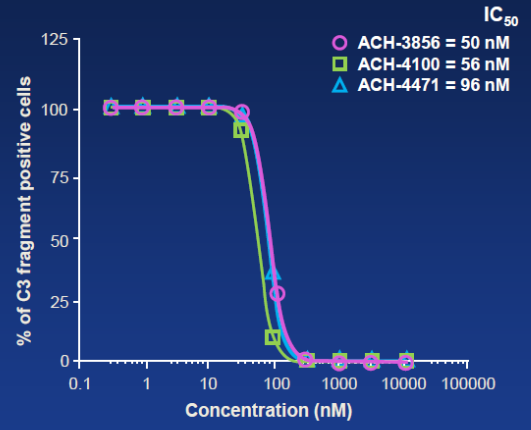
NIH U.S. National Library of Medicine
ClinicalTrials.gov

Dose-dependent Inhibition of Hemolysis and C3 Deposition on Rabbit Erythrocytes

Hemolysis[1]

Compound ID	IC_{50} ± SD (nM)	IC_{90} ± SD (nM)	N
ACH-4471	17 ± 11	70 ± 23	6
ACH-4100	17 ± 6.4	45 ± 15	8
ACH-3856	8.7 ± 3.9	22 ± 8.9	40

C3 Deposition[2]



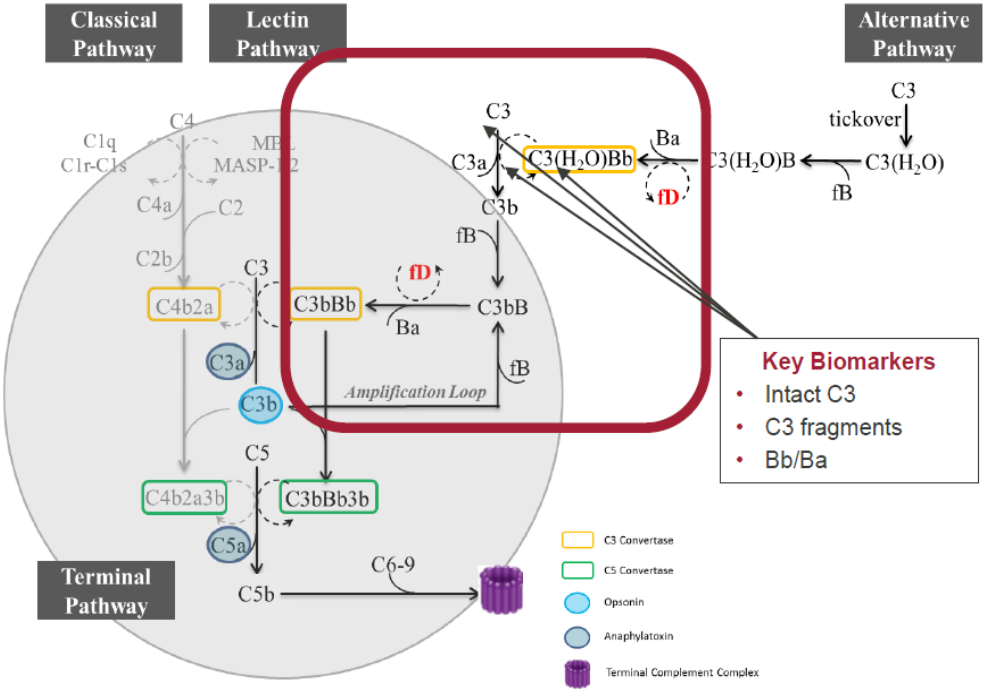
1. Incubation with Normal Human Serum (NHS)

2. Incubation with C5-depleted NHS

A Proof of Concept Study for a 12 Month Treatment in Patients With C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Factor D Inhibitor for the Treatment of C3G



Key Biomarkers

- Intact C3
- C3 fragments
- Bb/Ba

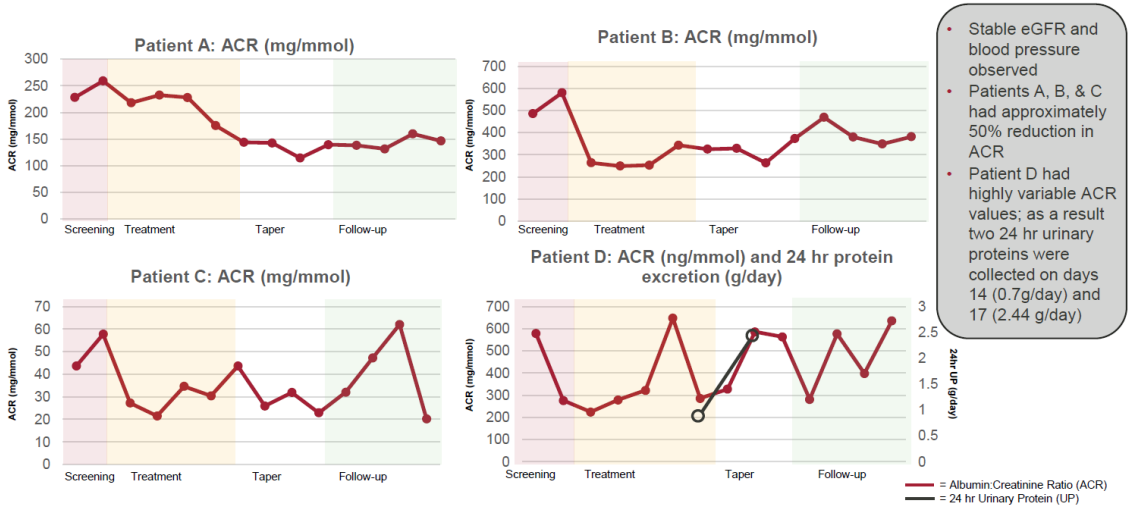
C3G: A Disease of Alternative Pathway (AP) Hyperactivity

- Increased consumption of intact C3
- Excess production of C3 fragments
- C3 fragments deposited in glomeruli

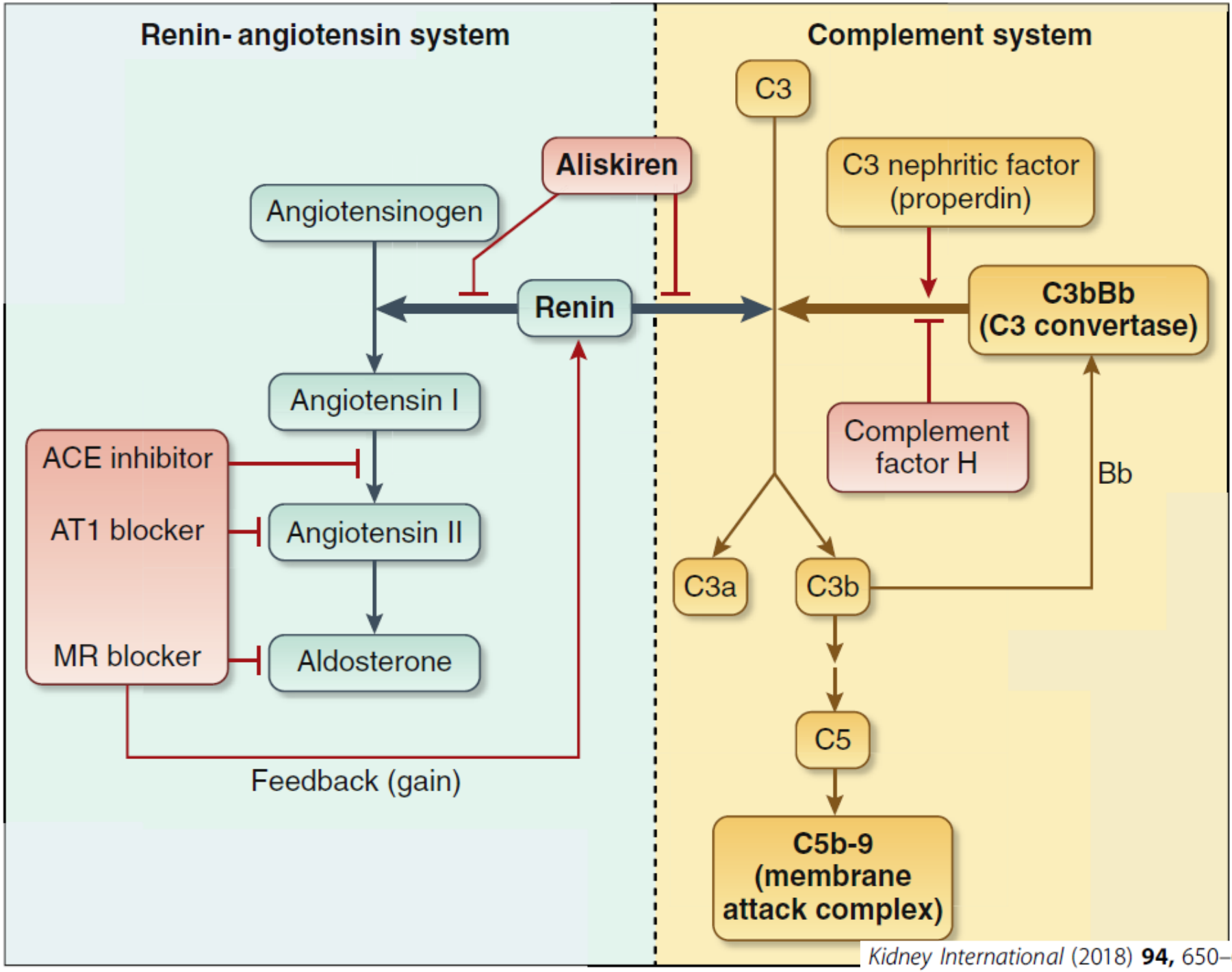
ACH-4471: An AP Inhibitor

- ACH-4471 is the first drug designed to target the underlying pathophysiology of C3G
- ACH-4471 inhibits factor D, selectively reducing AP activity
- Reduction of AP hyperactivity should prevent further glomerular C3 deposition

Reduction in ACR with 14-Day ACH-4471 Treatment

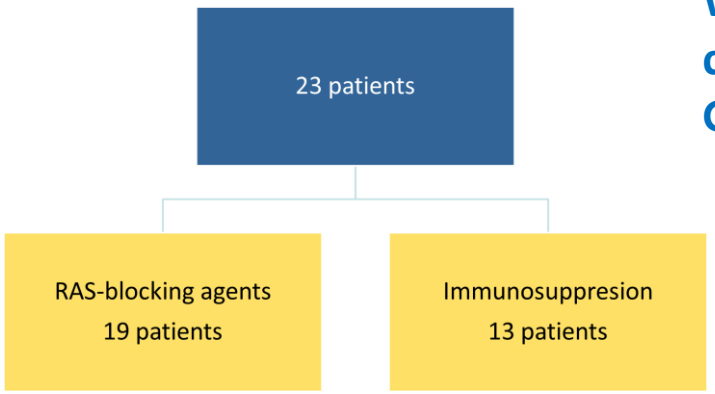


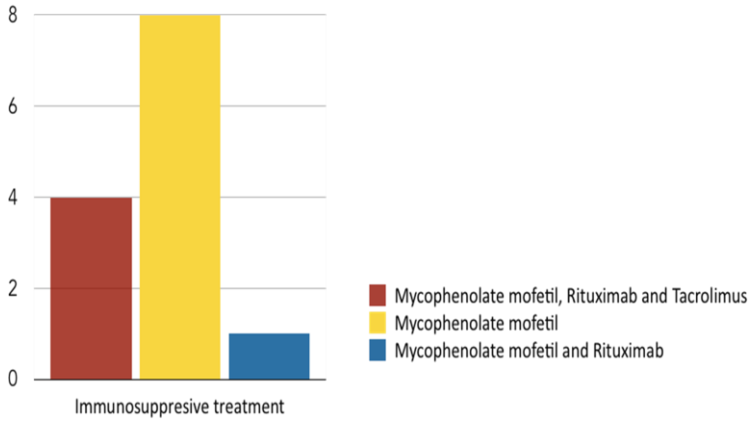
- Stable eGFR and blood pressure observed
- Patients A, B, & C had approximately 50% reduction in ACR
- Patient D had highly variable ACR values; as a result two 24 hr urinary proteins were collected on days 14 (0.7g/day) and 17 (2.44 g/day)

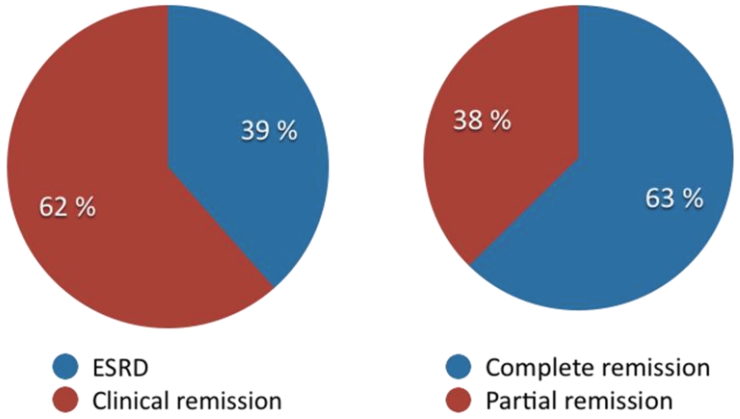


Kidney International (2018) **94,** 650–652

What is the best treatment for Immune-complex mediated Membranoproliferative Glomerulonephritis?







	n=23
Age, years (mean, SD)	41± 25 (10-81)
Elderly patients (> 65 years)	26 %
Sex (male/female) (%)	56.5/43.5%
Clinical presentation, n (%) a)Nephrotic syndrome b)Nephritic syndrome c)Proteinuria d)Other	14 (60.8%) 2 (8.7%) 5 (21.7%) 2 (8.7%)
Baseline SCr (mg/dl) (mean, SD)	1.4 ± 0.82 (0.60-3.66)
Baseline eGFR-MDRD (ml/min/1.73m^2) (mean, SD)	73 ± 39.8 (12.1-142)
Acute kidney injury (%)	48 %
Proteinuria (g/day) (mean, SD)	4.3 ± 3.1 (0.10-12.0)
Microhaematuria (%)	100 %
Hypocomplementemia, n (%) a)No b)C3 c)C3 and C4	8 (38.1%) 6 (28.6%) 7 (33.3%)

A Proof of Concept Study for a 12 Month Treatment in Patients With C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN). Factor D inhibitor

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Morales E et al, unpublished

Atypical postinfectious glomerulonephritis is associated with abnormalities in the alternative pathway of complement

Sanjeev Sethi[1], Fernando C. Fervenza[2], Yuzhou Zhang[3], Ladan Zand[2], Nicole C. Meyer[3], Nicolò Borsa[3], Samih H. Nasr[1] and Richard J.H. Smith[3,4,5]

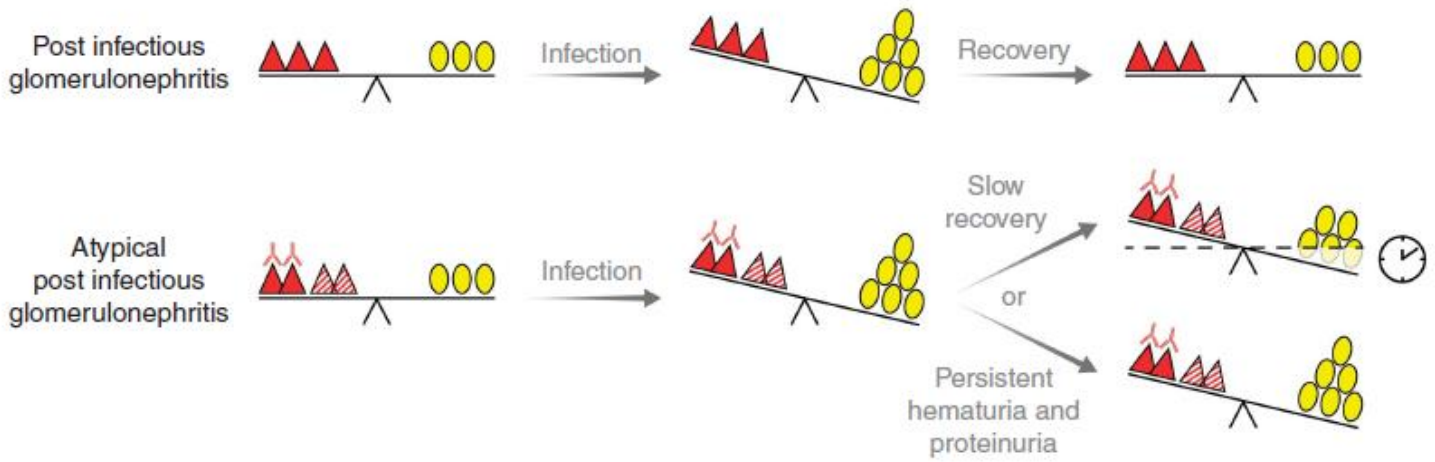


Table 3 | Complement abnormalities

Patient	*CFH*	*CFHR5*	FH antibodies[a]	Hemolytic assay[b]	APFA[c]	C3NeF	sMAC[d]
1	c.2171delC, p.Thr724fsX, 725	No mutations	Negative	ND	ND	Negative	0.24 mg/l
2	No mutations	c.646-647, AA>TT, p.Asn216Phe	Negative	0%, Normal	63%, Abnormal	Negative	0.21 mg/l
3	No mutations	No mutations	Negative	1%, Normal	63%, Abnormal	Positive (C3CSAP[e])	ND
4	No mutations	No mutations	Negative	0%, Normal	1% Abnormal	Positive (IFE)	1.23 mg/l
5	No mutations	No mutations	Negative	12% Abnormal	34% Abnormal	Positive (IFE)	0.48 mg/l
6	No mutations	No mutations	Negative	0%, Normal	14% Abnormal	Positive (both assays)	ND
7	c.3350A>G, p.Asn1117Ser	No mutations	Negative	0% Normal	80%	Negative	ND
8	No mutations	No mutations	Negative	0% Normal	123%	Negative	0.13 mg/l
9	No mutations	No mutations	Negative	9% Abnormal	77%	Positive (both assays)	ND
10	c.1699A>G, p.Arg567Gly	No mutations	Negative	0%, Normal	0% Abnormal	Positive (both assays)	2.03 mg/l
11	No mutations	No mutations	Negative	0%, Normal	130%	Positive (C3CSAP)	0.21 mg/l

Thrombotic microangiopathy associated with monoclonal gammopathy

Aishwarya Ravindran[1], Ronald S. Go[1], Fernando C. Fervenza[2] and Sanjeev Sethi[3]

Table 5 | Treatment and renal outcomes at follow-up of patients with TMA and monoclonal gammopathy

146 TMA

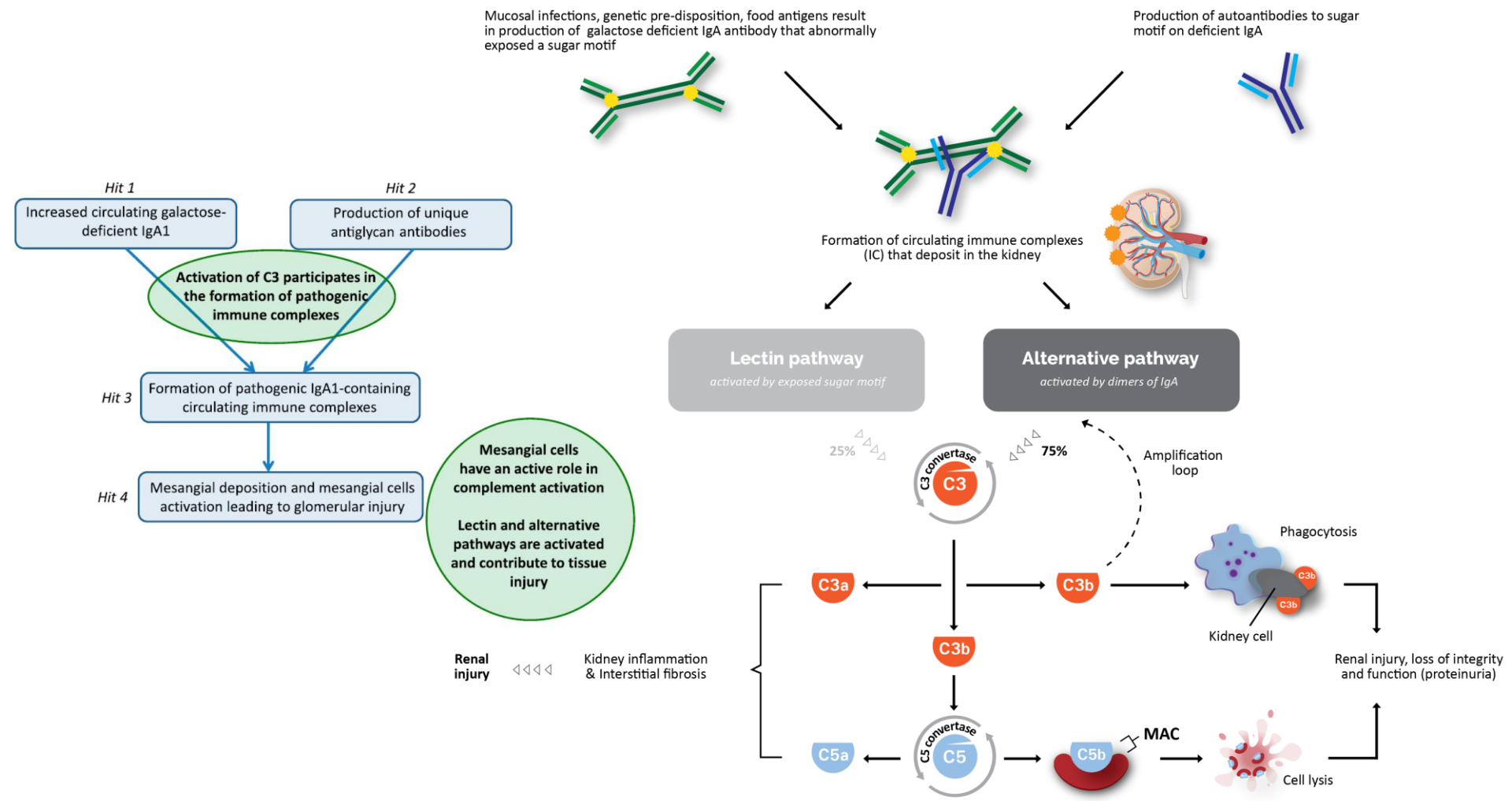
13,7%

Patient	Therapy	Time to final follow-up (months)	Serum creatinine (mg/dl) at diagnosis	eGFR at diagnosis	Serum creatinine at final follow-up mg/dl	eGFR at final follow-up	κ/λ ratio at final follow-up
1	TPE/steroid/rituximab	302.4	6.0	10	1.1	>60	35.6
2	TPE/steroid	60.4	1.2	>60	1.0	>60	0.41
3	Steroid	8.1	1.3	42	2.8	17[a]	1.29
4	Eculizumab[b]/steroid, cyclophosphamide/bortezomib-lenalidomide	41.7	1.7	41	1.4	52	1.16
5	TPE/dialysis	12.2	14	3	1.6	44	2.94
6	Thalidomide/steroid/dialysis	127.2	1.2	>60	On dialysis	On dialysis	1.27
7	TPE/steroid, rituximab, cyclophosphamide, IVIG, MMF/dialysis	119.0	7.4	2	Posttransplantation	Posttransplantation	0.46
8	TPE/rituximab, steroid, MMF, IVIG, bortezomib/dialysis	69.2	5	12	On dialysis	On dialysis	1.36
9	Dialysis	16.8	6.5	6	Posttransplantation	Posttransplantation	2.24
10	TPE/dialysis	53.2	5.1	9	On dialysis	On dialysis	NA
11	TPE/dialysis	1.4	8.4	6	On dialysis	On dialysis	0.03
12	None	0.3	1.8	39	1.7	42	NA
13	TPE/steroid, cyclophosphamide, MMF, azathioprine, rituximab/dialysis	69.7	2.0	28	On dialysis	On dialysis	0.65
14	TPE/rituximab, steroid	27.1	0.7	>60	1.0	55	NA
15	Steroid	1.7	4.8	12	4.8	12[c]	NA
16	Steroid	8.9	2.3	29	2.1	32	32.0
17	Dialysis	55.0	2.1	23	On dialysis	On dialysis	1.61
18	TPE/dialysis	160.8	3.5	13	0.8	>60	NA
19	Rituximab, cyclophosphamide, steroid	27.7	2.2	30	2.1	31	1.61
20	TPE/steroid, rituximab, dialysis	29.5	5.7	10	On dialysis	On dialysis	7.75

(2 TTP, 9 aHUS, Unclassified)

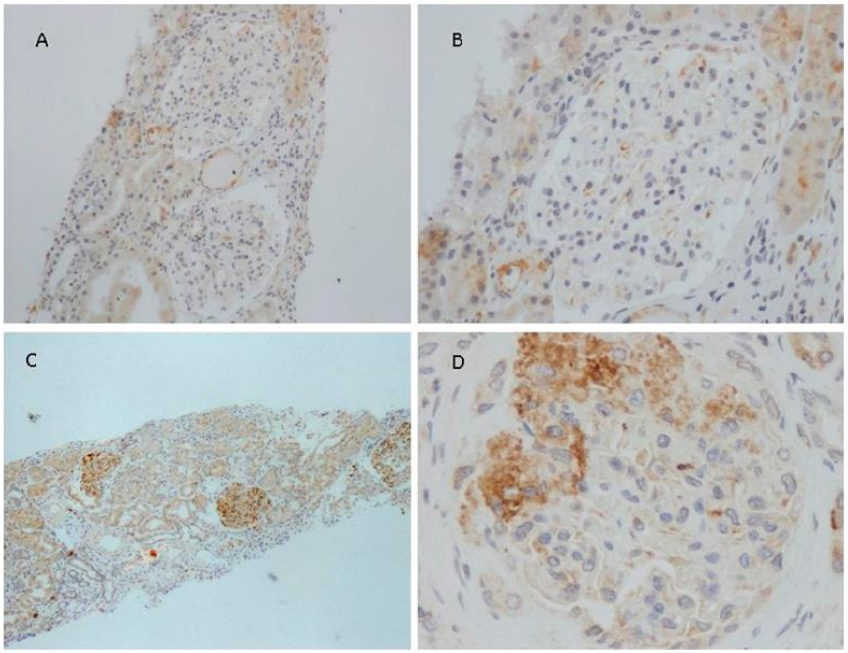
Kidney International (2016)

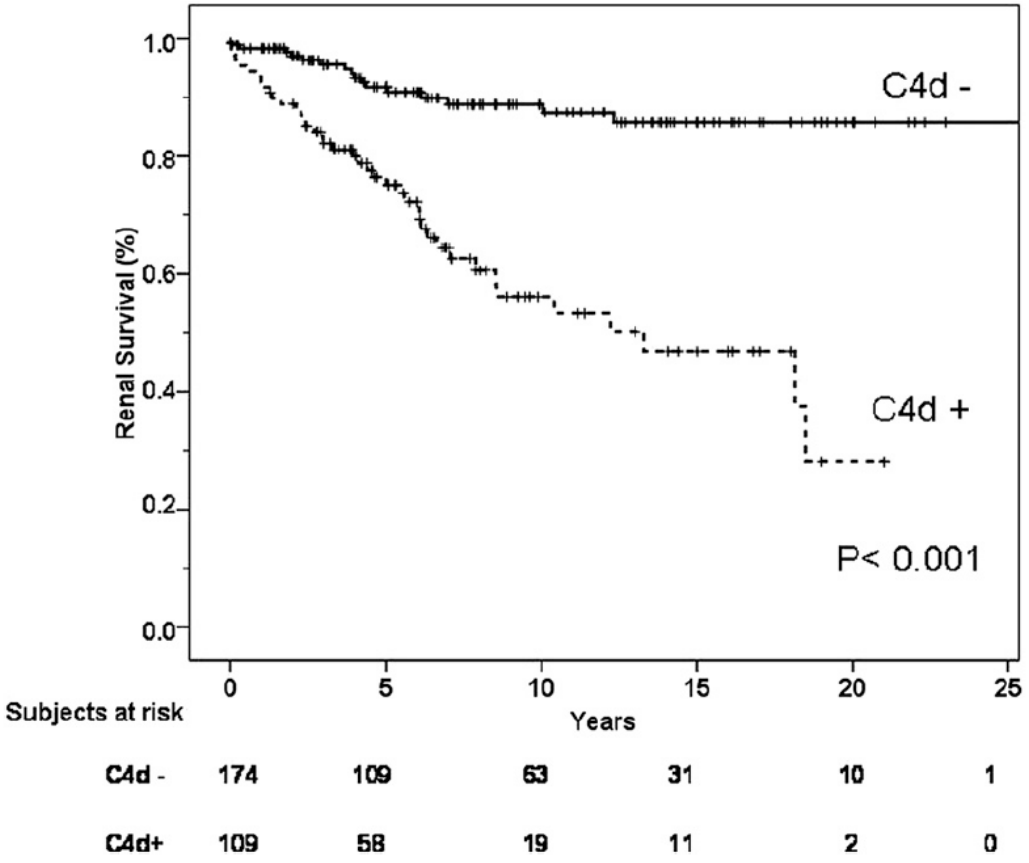
The Role of Complement in IgA Nephropathy (IgAN)



Association of C4d Deposition with Clinical Outcomes in IgA Nephropathy

283 patients with IgAN





Clin J Am Soc Nephrol 9: 897–904, 2014

Mesangial C4d Deposits in Early IgA Nephropathy

Alfons Segarra, Katheryne Romero,* Irene Agraz,* Natalia Ramos,* Alvaro Madrid,† Clara Carnicer,‡ Elias Jatem,§ Ramón Vilalta,† Luis Enrique Lara,† Elena Ostos,§ Naiara Valtierra,§ Juliana Jaramillo,* Karla V. Arredondo,* Gema Ariceta,† and Cristina Martinez‖*

Design, setting, participants, & measurements This retrospective cohort study included 190 patients with idiopathic IgA nephropathy diagnosed by kidney biopsy between 1988 and 2005. The patients had GFR≥80 ml/min per 1.73 m^2 at the time of diagnosis, and they had a paraffin-embedded kidney biopsy with eight glomeruli available.

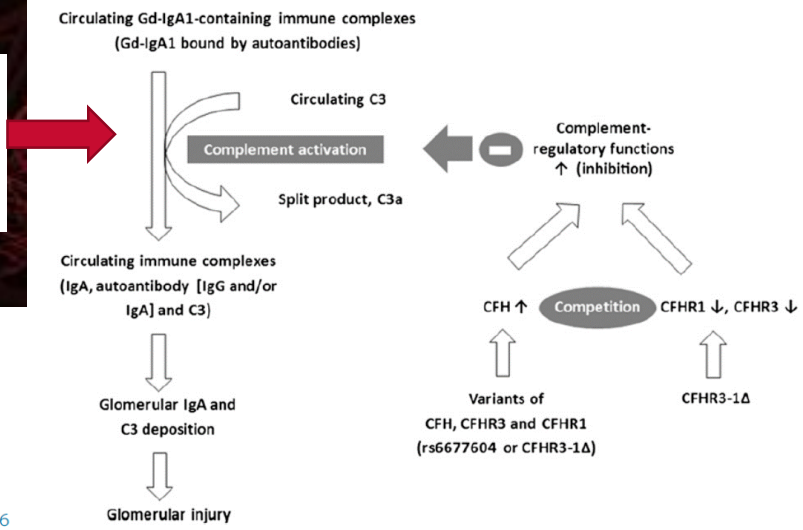
Table 4. Independent predictors of ESRD in the multivariate Cox regression analysis

Variables	Cox Multivariate Analysis	
	HR (95% CI)	*P* Value
Basal eGFR	0.69 (0.57 to 0.84)	<0.001
Smoking	1.04 (1.01 to 1.06)	0.04
Time-averaged proteinuria	3.12 (1.97 to 4.95)	<0.001
C4d+	2.07 (1.16 to 3.71)	0.02

Baseline eGFR is in milliliters per minute per 1.73 m^2, smoking is yes or no, time-averaged proteinuria is in grams per gram, and C4d positive is versus C4d negative. HR, hazard ratio; 95% CI, 95% confidence interval.

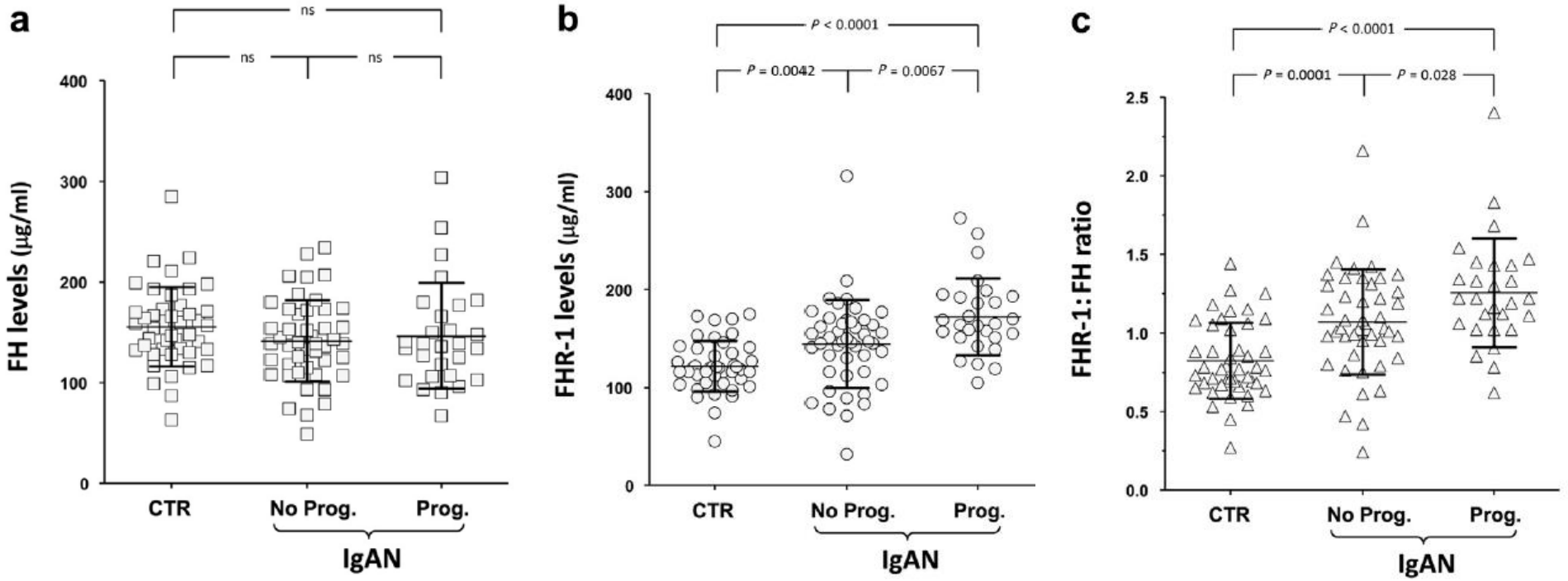
Clin J Am Soc Nephrol 2018; 13:258-264

Variants in Complement Factor H and Complement Factor H-Related Protein Genes, *CFHR3* and *CFHR1*, Affect Complement Activation in IgA Nephropathy



Elevated factor H-related protein 1 and factor H pathogenic variants decrease complement regulation in IgA nephropathy

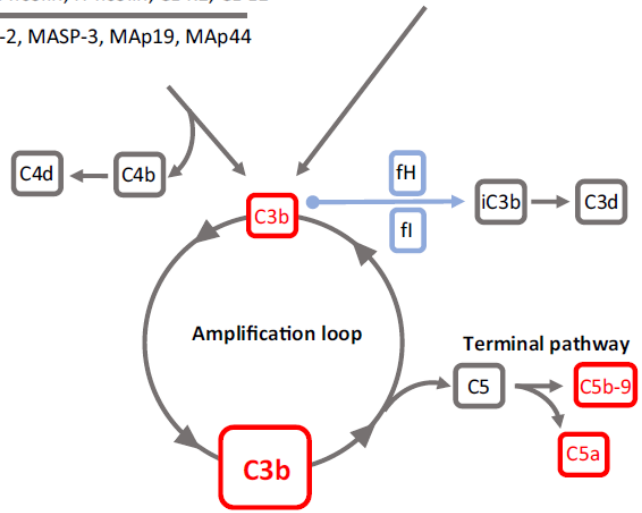
Agustín Tortajada[1,11], Eduardo Gutiérrez[2,11], Elena Goicoechea de Jorge[3,11], Jaouad Anter[1], Alfons Segarra[4], Mario Espinosa[5], Miquel Blasco[6], Elena Roman[7], Helena Marco[8], Luis F. Quintana[6], Josué Gutiérrez[3], Sheila Pinto[1], Margarita Lopez-Trascasa[9], Manuel Praga[2,10] and Santiago Rodriguez de Córdoba[1]



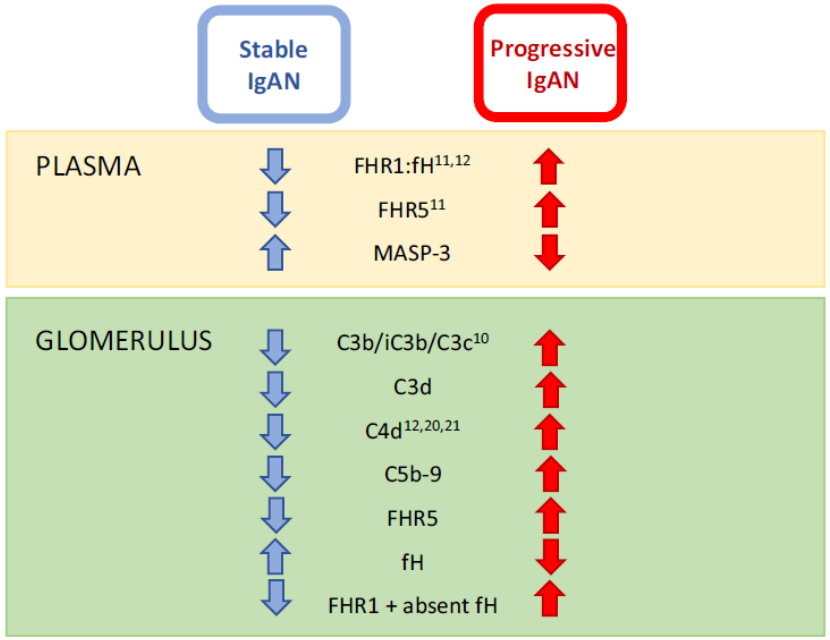
Kidney Int. 2017; 92(4):953-963

a

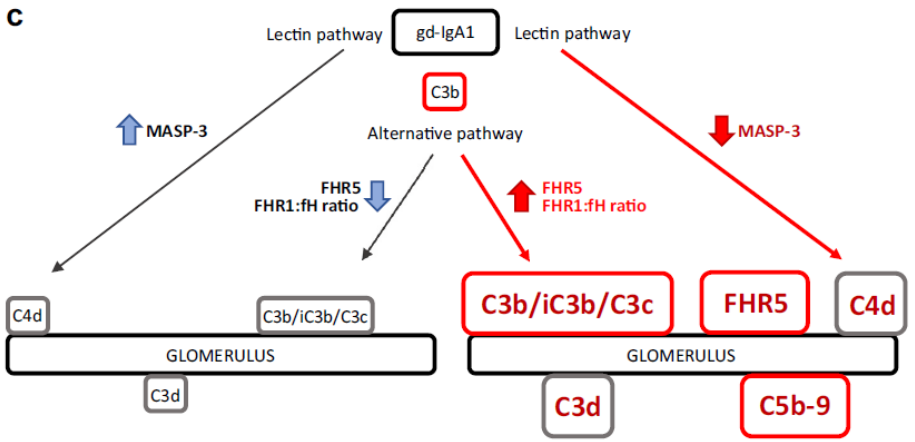
	Lectin pathway	Alternative pathway
Ligand	Carbohydrate / acetyl patterns	Spontaneous C3 hydrolysis
PRM	MBL, M-ficolin, L-ficolin, H-ficolin, CL-K1, CL-L1	
Pathway molecules	MASP-1, MASP-2, MASP-3, MAp19, MAp44	



b

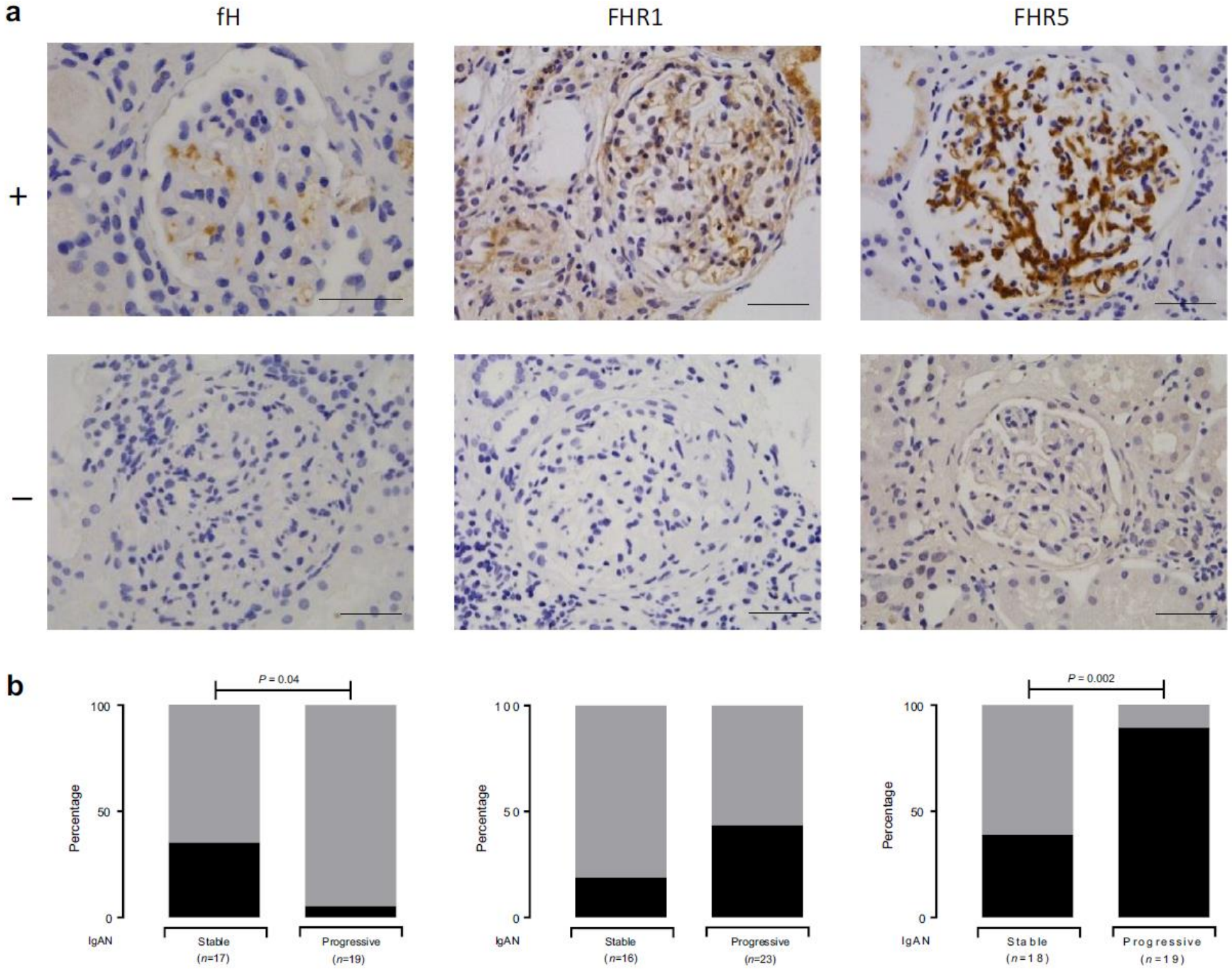


c



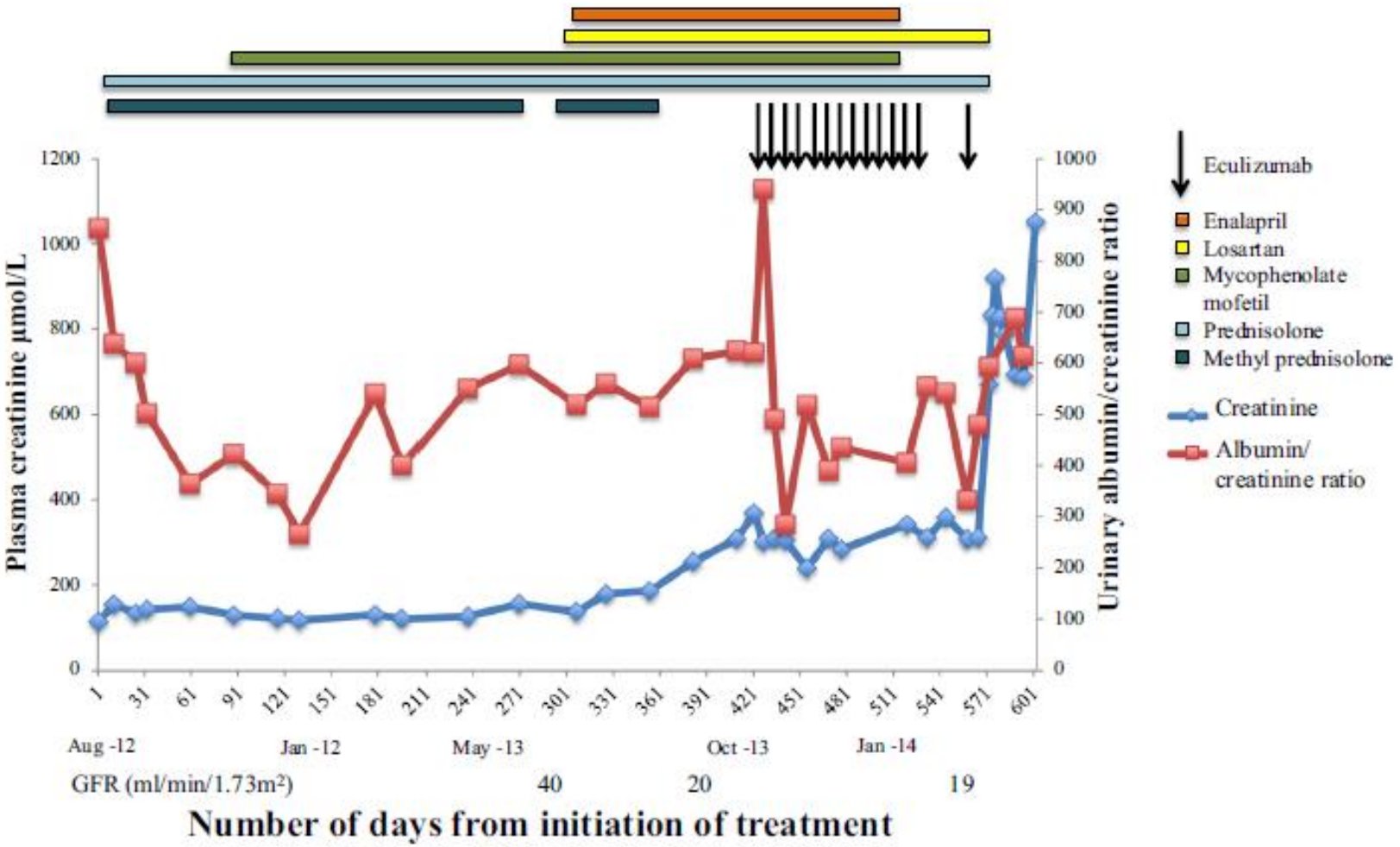
Stable IgAN | Progressive IgAN

IgAN severity	*CFHR3-1* copies	MBL deficient	C3b/iC3b/C3c	C3d	C4d	C5b9	fH	FHR1	FHR5
Stable	2	No	0	0	0	0.5	0	0	0
Stable	2	No	0	0.5	0.5	1	0.5	0.5	0
Stable	2	No	0.5	1	0	0	1		0.5
Stable	1	No	0.5	1	0	0	0	0.5	0
Stable	2	No	0.5	0.5	0	0.5	0.5	0	0.5
Stable	2	No	0.5		0.5	0		1	0
Stable	1	No	0.5	0.5	0.5	1	0	0.5	0.5
Stable	2	No	0.5	1	0.5	2	0	0.5	1
Stable	1	No	0.5	0.5	1	0.5	0.5	0.5	0.5
Stable	1	No	0.5	1	1	0.5	0	1	1
Stable	2	No	0.5	0		1		0.5	1
Stable	1	No	1	0	0	3	0.5	0	2
Stable	2	Yes	1		0.5		1	1	2
Stable	2	No	1	0.5	0.5	0.5	1		0.5
Stable	2	No	1	0.5	1	1	0	0.5	1
Stable	0	No	1	1	1	2	1	0	2
Stable	2	No	1	0	2	0	1	0.5	0
Stable	2	No	2	0.5	0.5	0	1	0	0.5
Stable	2	No			0		0.5		
Progressive	2	No	0.5					1	1
Progressive	2	No	0.5	1	1	1	0	2	1
Progressive	2	No	0.5	2	0.5	1	0	1	2
Progressive	2	No	0.5	1	1	2	0	0.5	2
Progressive	1	No	1		0.5			0	
Progressive	1	No	1	1				0	
Progressive	1	Yes	1	0.5	1	0.5	0	2	0.5
Progressive	2	No	1	0.5	1	0.5	0	2	
Progressive	2	Yes	1	1	1	1	0.5	1	1
Progressive	1	No	1		1	1		0.5	
Progressive	2	No	1	1	1	2	0	2	1
Progressive	2	No	1	1	1	2	0	0	1
Progressive	1	No	1	1	1	2	0.5	0	2
Progressive	0	No	1	1	2	2	0.5	0	2
Progressive	2	No	1	1	2	3	0	1	0
Progressive	1	No	2		0.5		0	1	2
Progressive	2	No	2		0.5	2	0	1	2
Progressive	1	No	2	2	1	2	0	0	3
Progressive	2	No	2	2	1	2	0	0.5	3
Progressive	2	No	2	2	1	3	0	0	3
Progressive	2	No	3	2	2	3	0	0	3
Progressive	2	No	3	1	1	3	0	0.5	3
Progressive	1	No	3	2	0.5	3	1	0	3

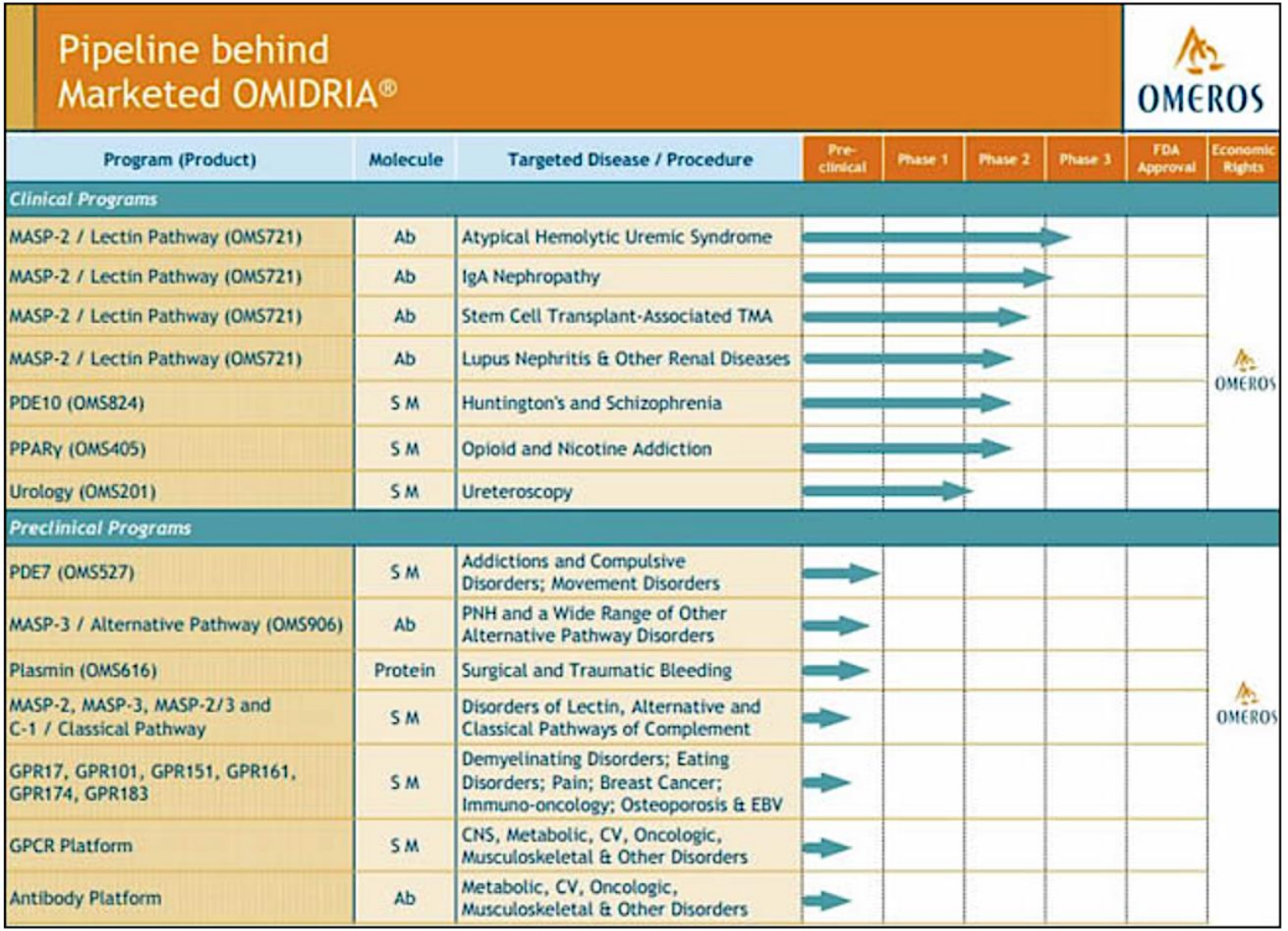

a
fH
FHR1
FHR5
+
–
b
P = 0.04
P = 0.002
100
50
0
Percentage
IgAN
Stable
(n=17)
Progressive
(n=19)
Stable
(n=16)
Progressive
(n=23)
Stable
(n=18)
Progressive
(n=19)

Eculizumab treatment for rescue of renal function in IgA nephropathy

Therese Rosenblad · Johan Rebetz · Martin Johansson · Zivile Békássy · Lisa Sartz · Diana Karpman



Pediatr Nephrol (2014) 29:2225–2228



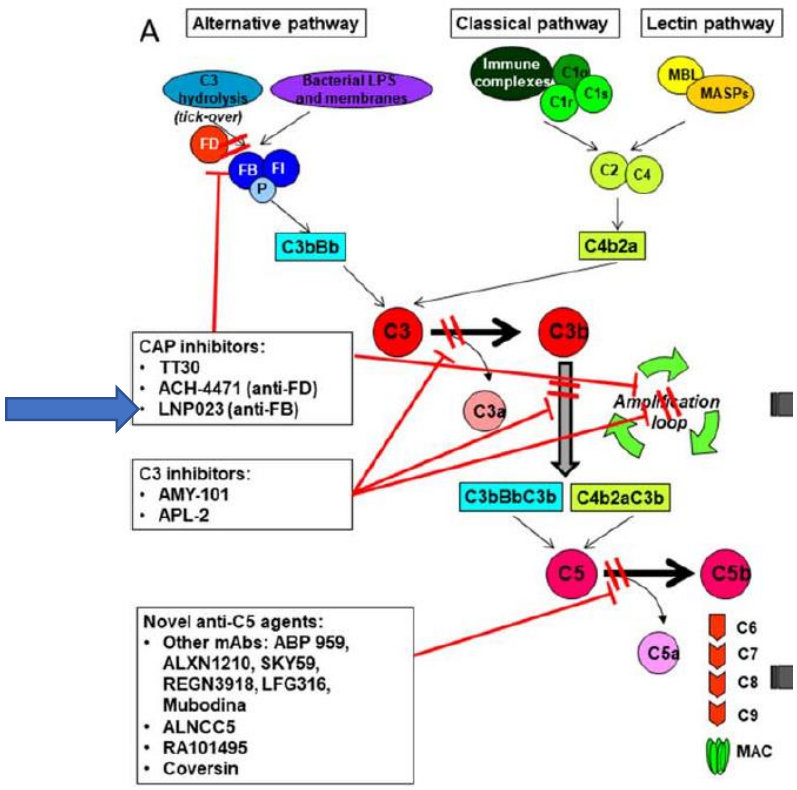
Study of the Safety and Efficacy of OMS721 in Patients With Immunoglobulin A (IgA) Nephropathy

NIH U.S. National Library of Medicine

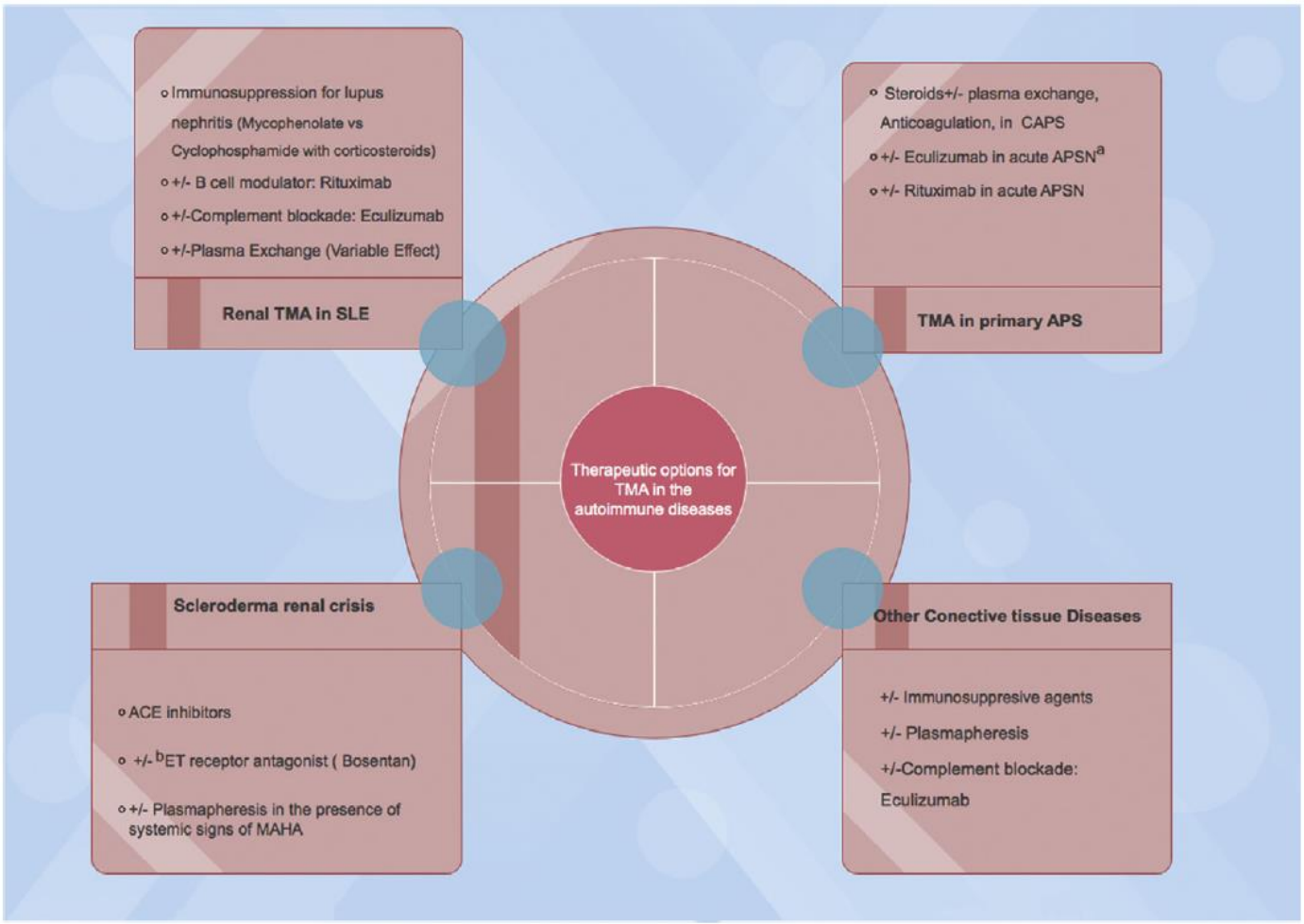
ClinicalTrials.gov

Study of Safety and Efficacy of LNP023 in Patients With Kidney Disease Caused by Inflammation (IgA nephropathy)

ClinicalTrials.gov Identifier: NCT03373461



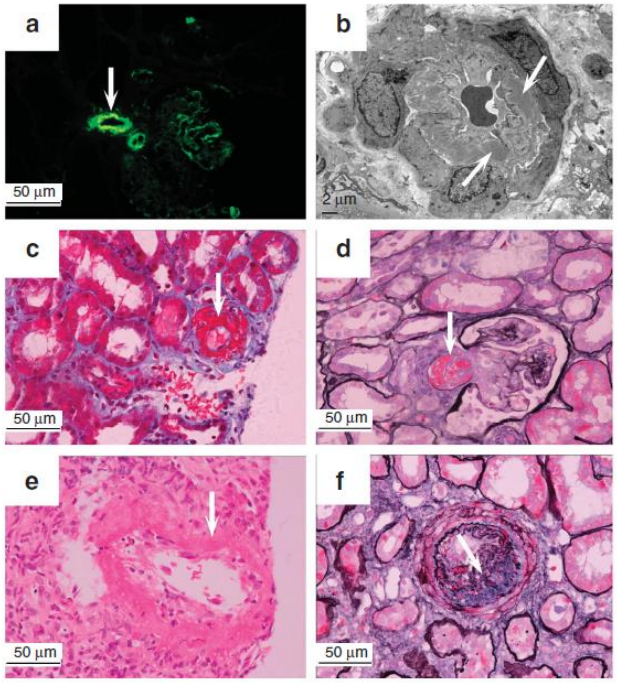
- Female and male patients above 18 years of age with a **biopsy-verified IgA nephropathy** and where the biopsy was performed within the prior three years.
- Patients must weigh at least 35 kg to participate in the study, and must have a body mass index (BMI) within the range of 15 - 38 kg/m2. BMI = Body weight (kg) / [Height (m)]2
- Measured Glomerular Filtration Rate (GFR) or estimated **GFR (using the CKD-EPI formula) ≥30 mL/min** per 1.73 m2
- **Urine protein ≥1 g/24hr** at screening and ≥0.75 g / 24h after the run- in period
- Vaccination against Neisseria meningitidis types A, C, Y and W-135 is required at least 30 days prior to first dosing with LNP023. Vaccination against N. meningitidis type B, S. pneumoniae and H. influenzae should be conducted if available and acceptable by local regulations, at least 30 days prior to first dosing with LNP023
- All patients must have been on supportive care **including a maximally tolerated dose of ACEi or ARB** therapy for the individual, antihypertensive therapy or diuretics for at least 90 days before dosing

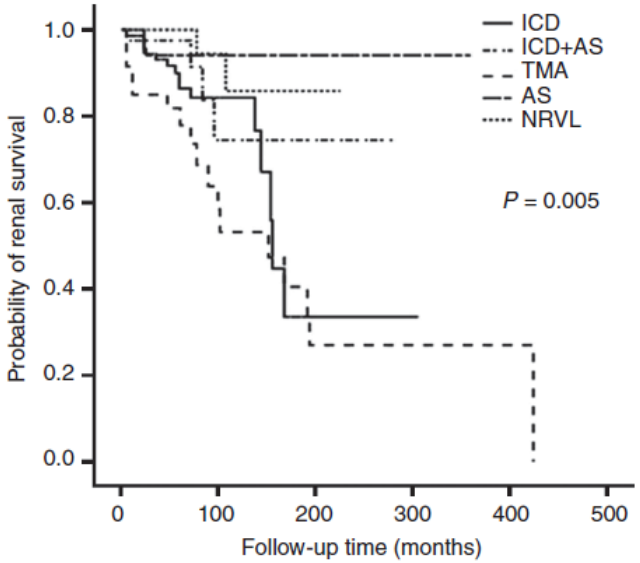


Rheum Dis Clin N Am 44 (2018) 635–649

Inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis improves renal outcome predictions

Li-Hua Wu[1,2,4], Feng Yu[1,4], Ying Tan[1], Zhen Ou[1], Meng-Hua Chen[2], Su-Xia Wang[1], Gang Liu[1] and Ming-Hui Zhao[1,3]





350 patients (82%) vascular lessions

Table 2 | Comparisons of clinical and laboratory data in patients with and without renal vascular lesions in lupus nephritis

	ICD	TMA	AS	ICD + AS	NRVL	*P*-value[a]
Number of patients	149	60	23	41	62	
Gender (male/female)	27/122	12/48	3/20	2/39	11/51	0.227
Age (mean ± s.d.) (years)	32.7 ± 11.8	31.6 ± 10.8	33.2 ± 8.5	36.3 ± 9.8	31.6 ± 12.4	0.149
Number with hypertension (blood pressure ⩾140/90 mm Hg) (%)	74 (49.7) *,#	44 (74.6)▲,●	9 (40.9)	24 (58.5)▼	22 (35.5)	<0.001
Number with neurological disorder (%)	14 (9.4)	8 (13.3)	1 (4.3)	1 (2.4)	2 (3.2)	0.160
Number with anemia (%)	109 (73.2)#	51 (85.0)▲,●	13 (56.5)	29 (70.7)▼	27 (45.0)	<0.001
Number with thrombocytopenia (%)	39 (26.2)	27 (45.0)	10 (43.5)	13 (31.7)	17 (28.3)	0.067
Number with hematuria (%)	119 (79.9)#	53 (88.3)▲,●	16 (69.6)	32 (78.0)	37 (59.7)	0.003
Number with acute renal failure (%)	28 (28.0)*	29 (60.4)▲,▽,●	3 (27.3)	5 (12.2)	7 (18.9)	<0.001
SLEDAI (mean ± s.d.)	17.9 ± 5.5◆,#	18.9 ± 6.1 ▲,●	13.7 ± 3.9○	17.17 ± 4.99	15.8 ± 6.2	<0.001
Hemoglobin (mean ± s.d.) (g/l)	100.6 ± 24.5*,#	87.1 ± 21.6▲,▽,●	106.4 ± 33.5	102.2 ± 23.4▼	112.3 ± 21.7	<0.001
Urine protein (mean and range) (g/24 h)	4.1* (2.2, 6.3)	5.9● (3.5, 8.3)	5.3 (1.6, 8.9)	5.0 (0.2, 17.3)	3.7 (1.9, 6.4)	0.028
Serum creatinine (mean and range) (μmol/l)	81.0*,# (67.0, 114.5)	169.0▲,▽,● (98.5, 287.8)	78.0 (65.0, 97.0)	103.9▼ (50.0, 280.0)	73.0 (59.0, 89.0)	<0.001
C3 (mean ± s.d.)	0.47 ± 0.23◆,#	0.41 ± 0.19▲,●	0.59 ± 0.21○	0.43 ± 0.26▼	0.54 ± 0.30	0.006
Number with positive ANA (%)	148 (99.3)	59 (98.3)	22 (95.7)	41 (100)	60 (96.8)	0.218
Number with positive anti-dsDNA antibodies (%)	111 (75.0)◆,#	44 (73.3)▲,●	10 (43.5)	25 (61.0)	28 (45.9)	<0.001
Number with positive aCL antibodies (%)	9 (10.1)	1 (2.8)	1 (6.2)	3 (7.3)	5 (14.7)	0.467

The spectrum of renal thrombotic microangiopathy in lupus nephritis

Song *et al. Arthritis Research & Therapy* 2013, **15**:R12

Table 5 Comparison of treatment data between lupus nephritis patients with and without renal TMA

	LN with renal TMA	LN without renal TMA	*P*-value
Number of patients (%)	36	112	
Treatment	**24.3%**		
PE (Number of patients (%))	19 (52.8)	7 (6.25)	<0.001
MP (Number of patients (%))	26 (72.2)	18 (16.1)	<0.001
P	36 (100)	112 (100)	1
CYC	30 (83.3)	88 (78.6)	0.536
AZA	1 (2.8)	5 (4.5)	1
MMF	3 (83.3)	11 (9.8)	1
LEF	2 (5.6)	8 (7.1)	1
Treatment response			
CR	8 (22.2)	30 (26.8)	0.586
PR	12 (33.3)	65 (58.0)	0.01
TF	16 (44.4)	17 (15.2)	<0.001
Duration of follow-up (m)	53 (6,240)	53 (6,282)	0.15
Relapse rate	4 (4/20, 20%, 3 with nephritic relapse and 1 with proteinuric relapse)	17 (17/95, 17.89%, 15 with nephritic relapse and 2 with proteinuric relapse)	0.543

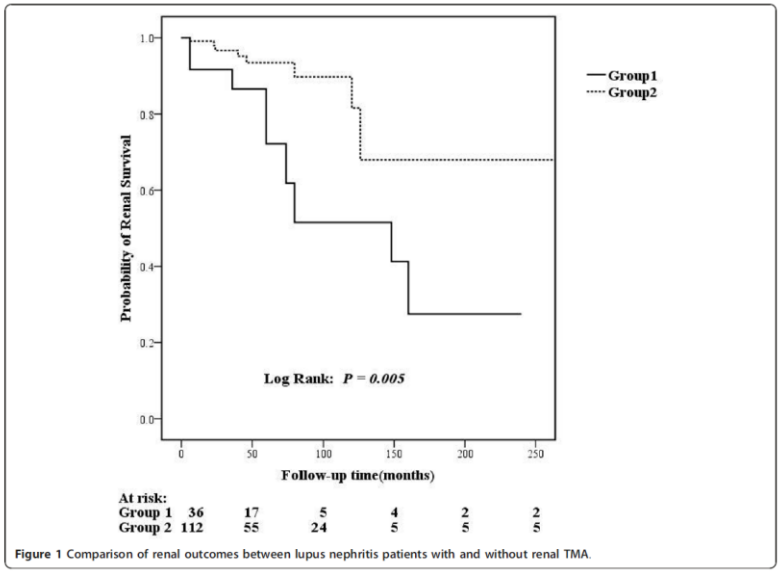


Figure 1 Comparison of renal outcomes between lupus nephritis patients with and without renal TMA.

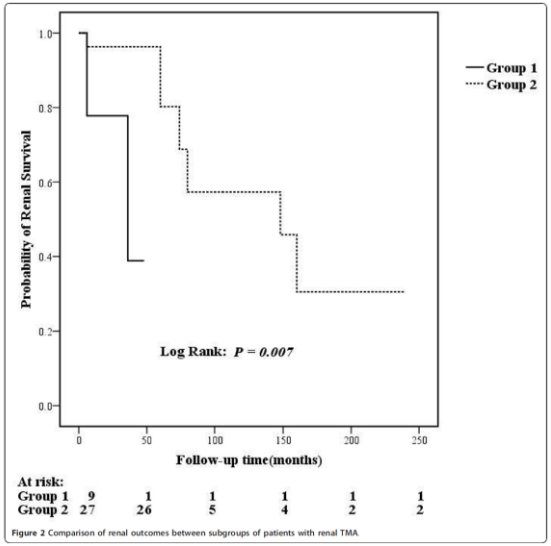


Figure 2 Comparison of renal outcomes between subgroups of patients with renal TMA.

C4d, FH

Use of eculizumab in a systemic lupus erythemathosus patient presenting thrombotic microangiopathy and heterozygous deletion in CFHR1-CFHR3. A case report and systematic review

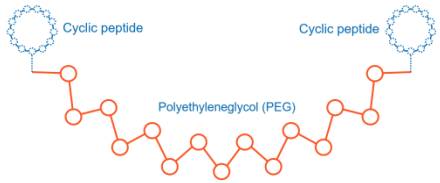
Maria Izabel de Holanda[1] · Luis Cristóvão Pôrto[2] · Teresa Wagner[1] · Luis Fernando Christiani[1] · Lilian M. P. Palma[3]

Case report studies	Gender	Ethnics	Age	Diag	TMAs (y/N)	Plx/session	RxMab	Igg	Time (days) of start ECU	Hemato resp	Renal resp	Genetics	STOP ECU/doses	Relapses
Hadaya et al. 2011 [13]	F	ND	27	SLE	N/in the graft	Y/8	Y/1 dose pre tx	N	12	Y	Y/21 days	No Mutation	Y/5	N
Shapira et al. 2012 [14]	M	ND	28	SLE/APS	Y	Y/60	Y	Y/5doses	300	Y	Y	ND	N	N
Canaud et al. 2013 [15]	F	Caribbean	36	SLE/APS	Y	Y/60	N	N	14	Y/10 days	Y/21 days	ND	Y/28	N
	F	Caucasian	35	SLE/APS	Y	Y/14	N	N	14	Y/10 days	Y/14 days	ND	Y/9	N
	M	ND	33	SLE/APS	Y	Y/30	N	N	30	Y/10 days	Y/14 days	ND	Y/8	N
Kronbichleret al. 2014 [16]	F	ND	30	SLE/APS	Y	Y/12	Y/4 doses	N	35	Y	N	Mutation exon 13 C3 gene	Y/9	N
Strakhan et al. 2014 [8]	F	ND	36	APS	Y	Y/15	N	N	56	Y	Y	Not done	N/10	N
Lonze et al. 2014 [9]	ND	ND	51	APS	Y	N	Y/1 dose	N	−1	Y	Y	ND	N	N
	ND	ND	39	APS	N	Y/4 before	Y/1 dose	N	−1	Y	Y	ND	N	N
	ND	ND	38	APS	N	Y/4 before	Y/1 dose	N	−1	Y	Y	ND	N	N
Bakhtar et al. 2014 [18]	M	ND	26	SLE/APS	Y	Y/5	N	N	7	Y	Y	No Mutation	N	N
Coppo et al. 2014 [17]	F	Moroccan	4	SLE	Y	Y/9	Y/2 doses	N	60	Y/7 days	Y/21 days	No mutation	Y/relapse/continuous	Y
Zikos et al. 2015 [19]	M	ND	46	APS	Y	Y/24	Y/3 doses	Y/1dose	72	Y	N	No mutation	Y/35	N
Wig et al. 2015 [20]	F	ND	48	APS	Y	Y/120	Y/2 doses	Y/5doses	180	Y/42 days	NI	ND	N	N
El-Husseini et al. 2015 [21]	F	AA	24	SLE	Y	Y/8	N	N	37	Y	Y/14 days	Not done	Y/14	N
Pickering et al. 2015 [22]	F	Caucasian	17	SLE	N	N	Y/4 doses	N	300	Y	Y/30 days	Not done	Y/6	N
Raufi et al. 2016 [23]	F	Vietnamese	25	SLE	Y	Y/18	Y/2 doses	N	49	Y/56 days	Y/90 days	No mutation	ND	ND
Bermea et al. 2016 [24]	F	AA	30	SLE	Y	Y/5	Y/1 dose	Y/3 doses	200	Y/44 days	N	ND	Y/6	N
	M	Hispanic	21	SLE	Y	Y/20	Y/3 doses	Y/3 doses	40	Y/7 days	N	ND	N	N
Geethakumari et al. 2017 [25]	M	Caucasian	58	SLE/APS	N	Y/2	N	N	15	Y/60 days	Y/60 days	No mutation	N	N

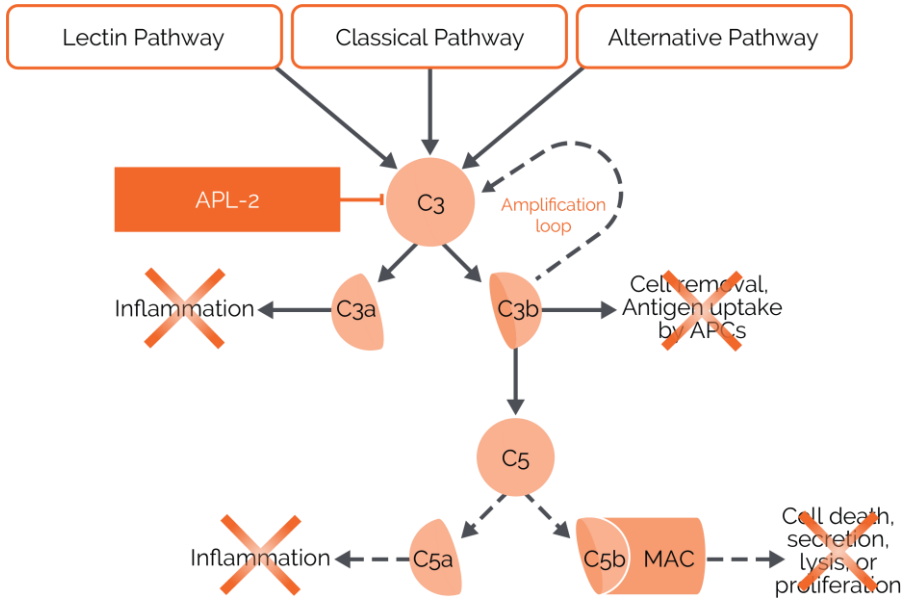
Clin Rheumatol 2017;36:2859-2867

Discovery (APL2-201): Phase 2 Clinical Trial of APL-2 Therapy in Patients with IgAN, LN, Primary MN, and C3G

A phase 2 study to evaluate the safety and biologic activity of APL-2 in patients with IgA nephropathy (IgAN), lupus nephritis (LN), primary membranous nephropathy (Primary MN), or C3 glomerulopathy (C3 glomerulonephritis or dense deposit disease)



APL-2 is a PEGylated cyclic peptide inhibitor of complement C3.



Objectives

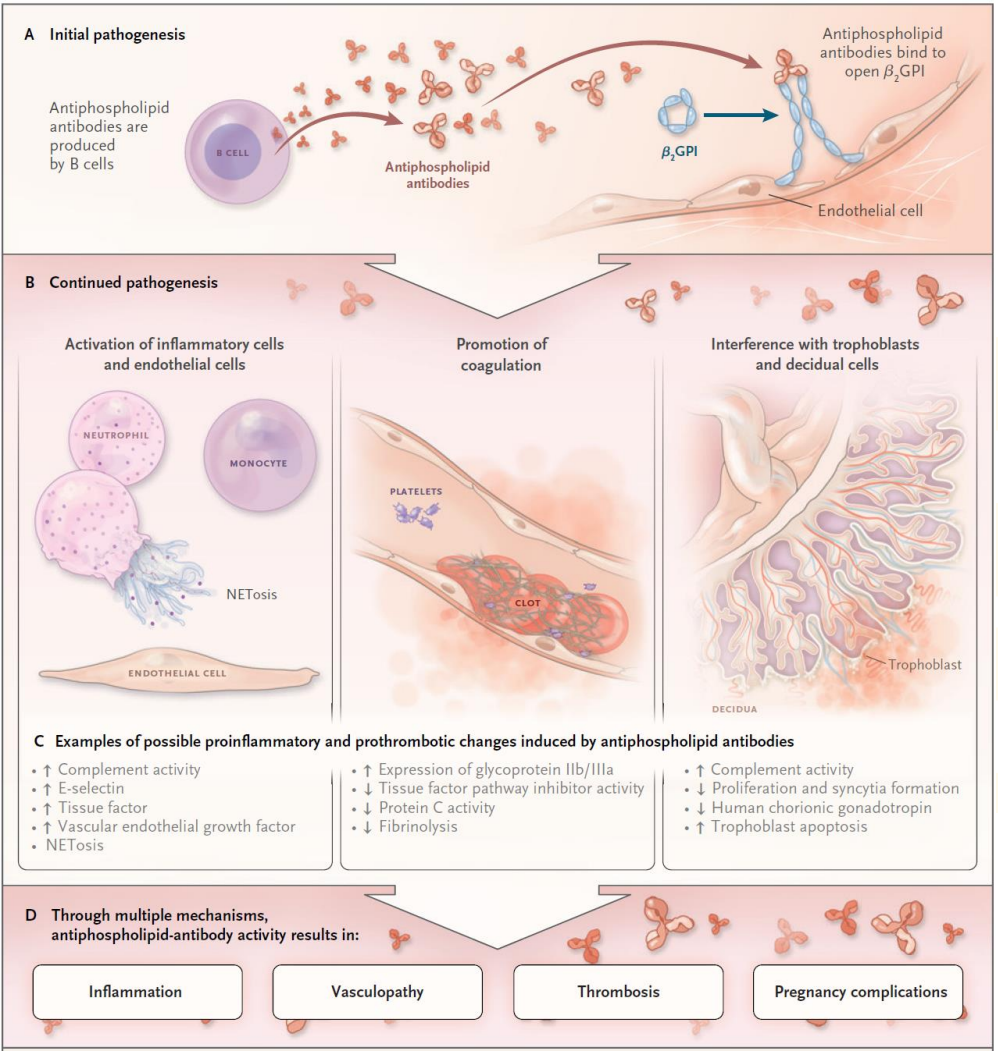
This is a prospective, phase 2 open-label study, consisting of a single cohort with a total of approximately 48 subjects with a diagnosis of 1 of the 4 complement-mediated nephropathies: IgAN, LN, primary MN, or C3G (~12 subjects per disease).

The planned length of participation in the study for each subject is up to 52 weeks, including a screening period, a 16-week treatment period, and a 24-week follow-up period.

Primary Objective

The primary objectives of this study are to establish preliminary efficacy and safety of the investigational drug APL-2 in patients with IgAN, LN, primary MN, and C3G.

Diagnosis and Management of the Antiphospholipid Syndrome



Intravenous immune globulin	Part of first- or second-line combination treatment for catastrophic APS (1–2 g/kg, given over a period of 3–5 days); first- or second-line treatment for severe thrombocytopenia (1 g/kg; can repeat once, usually 1–2 days after first dose)
Plasma exchange	Part of first- or second-line combination treatment for catastrophic APS; for acute thrombotic microangiopathy in patients with aPL-related nephropathy
Traditional immunomodulatory agents (e.g., azathioprine, 100–150 mg per day, or mycophenolate mofetil, 1000–3000 mg per day)†	An option for severe thrombocytopenia, hemolytic anemia, or both; an option for aPL nephropathy
Sirolimus†	More data needed
Rituximab (e.g., 1000 mg on days 0 and 15, repeated every 6 mo)†	An option for thrombocytopenia, hemolytic anemia, livedoid vasculopathy, and aPL nephropathy; an option for catastrophic APS that is refractory to standard treatment
Eculizumab†	An option for catastrophic APS that is refractory to standard treatment; an option for acute thrombotic microangiopathy in patients with aPL-related nephropathy
Defibrotide†	More data needed

N Engl J Med 2018;378:2010-21

Microangiopatía trombótica secundaria y eculizumab: una opción terapéutica razonable

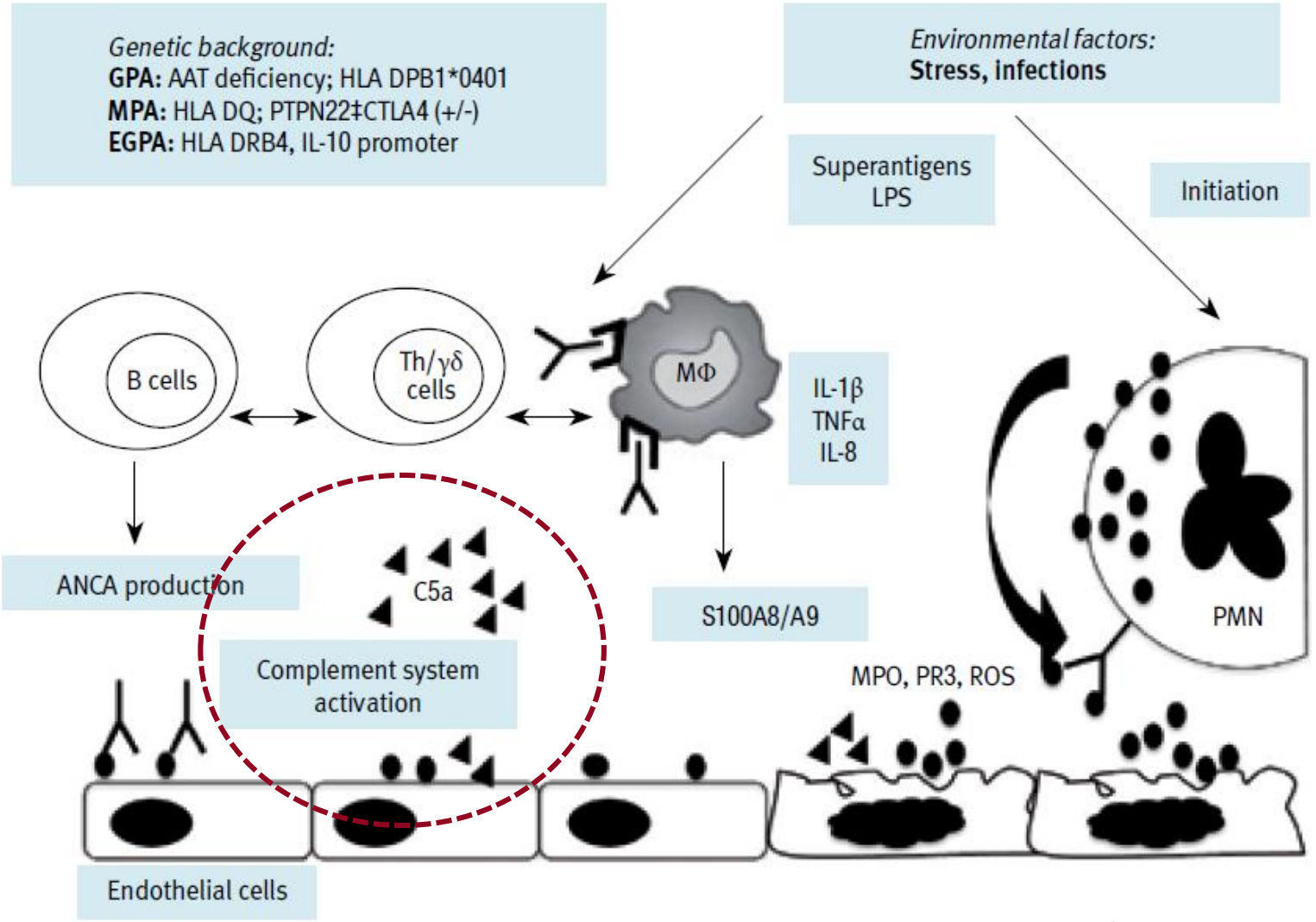
Elena Román[a,*], *Santiago Mendizábal*[a], *Isidro Jarque*[b], *Javier de la Rubia*[c], *Amparo Sempere*[b], *Enrique Morales*[d], *Manuel Praga*[d], *Ana Ávila*[e] y *José Luis Górriz*[e]

Tabla 3 – Utilización de eculizumab en MAT postrasplante de órgano sólido

Desencadenante	N	Duración del tratamiento	Resultado	Comentario
SAFC[24]	3	Continúan (1-4 años)	Estabilidad de función renal. Sin episodios de SAFC	Profilaxis de SAFC catastrófico. Inicio en el trasplante
SAFC[25]	1 (RP)	5 semanas	Resolución de la MAT y normalización de función renal a los 6 meses	Tratamiento de MAT 2.ª a SAF en el postrasplante
SAFC[26]	3 (RP)	3-12 meses	Resolución de la MAT y normalización de función renal	Respuesta rápida. Tras 2.ª dosis de eculizumab: resolución de MAT
SAFC[27]	1	7 meses	Resolución de la MAT	Lenta desaparición de MAT histológica
MAT postrasplante renopancreático[102]	1 (RP, reducción/retirada ICN)	2 semanas	Resolución de la MAT	Cese de diálisis tras la 1.ª dosis de eculizumab
MAT postrasplante cardiaco[105]	1 (RP, reducción/retirada ICN)	2 meses	Resolución de la MAT	Cese de diálisis, mejoría en función miocárdica y de alteraciones neurológicas
Trasplante intestinal (5) y hepático (2)[103]	7	4-107 semanas	Resolución de la MAT	Cese de diálisis en 3 de 4 pacientes
MAT postrasplante[104]	1 (RP, reducción/retirada ICN)	4 semanas	Resolución de la MAT	Respuesta tras 1.ª dosis de eculizumab, tras RP prolongado (18 sesiones)
MAT por ICN[101]	1 (RP, reducción/retirada ICN)	Una semana	Resolución de la MAT	
MAT asociada a CMV[88]	1 (RP)	3 meses	Resolución de la MAT	

Small-Medium Vessel Vasculitides: is the Complement System a Potential Forgotten Target?

Eleonora Ballanti MD, Maria S. Chimenti MD PhD and Roberto Perricone MD

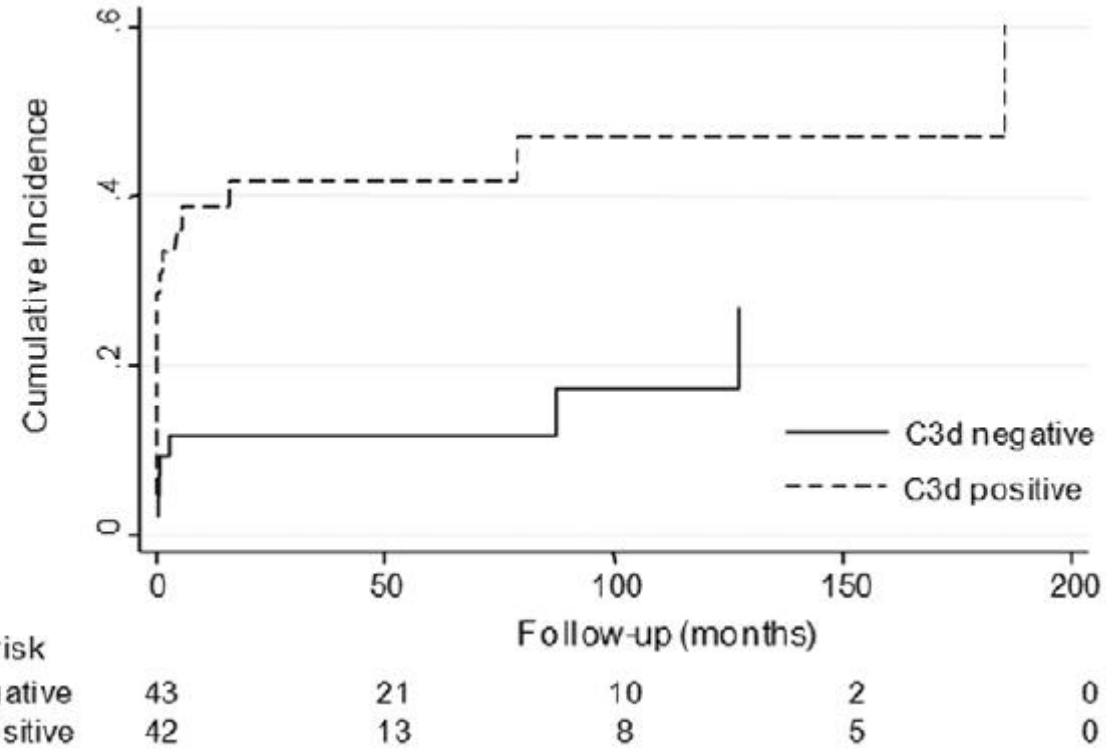


Isr Med Assoc J. 2015; 17(2):85-92.

Glomerular C3d as a novel prognostic marker for renal vasculitis☆

Javier Villacorta MD[a,*,1], Francisco Diaz-Crespo MD[b,1], Mercedes Acevedo MD[c], Carmen Guerrero MD[d], Yolanda Campos-Martin PhD[b], Eugenio García-Díaz MD[c], Manuela Mollejo PhD[b], Gema Fernandez-Juarez PhD[a]

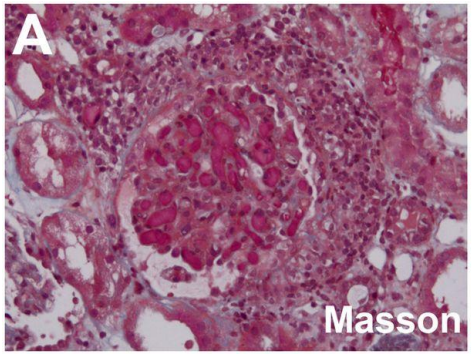
N=85 patients

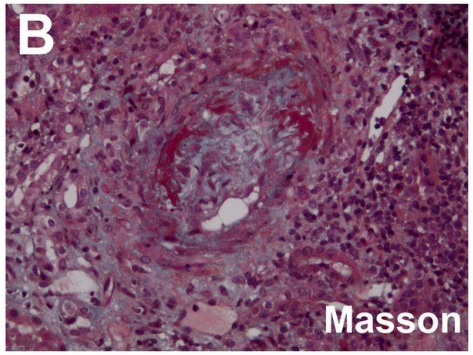


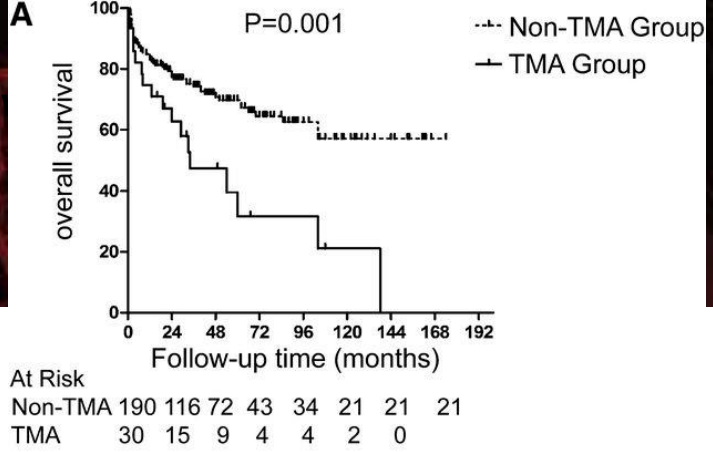
Human Pathology (2016) **56**, 31–39

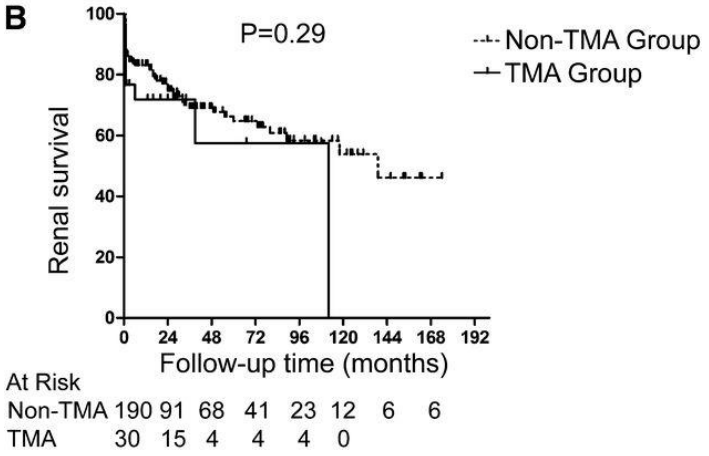
Clinicopathologic Characteristics and Outcomes of Renal Thrombotic Microangiopathy in Anti-Neutrophil Cytoplasmic Autoantibody-Associated Glomerulonephritis

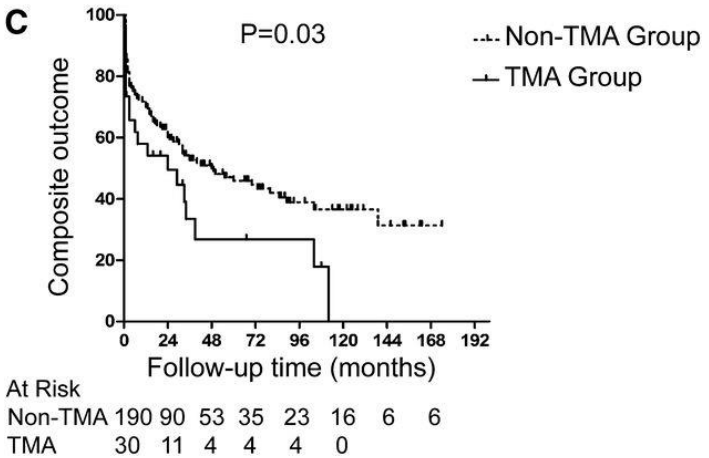
220 patients with ANCA-vasculitis. In 30 of them (13.6%) marked TMA histological lesions. Patients with superimposed TMA: More severe AKI, greater number of crescents







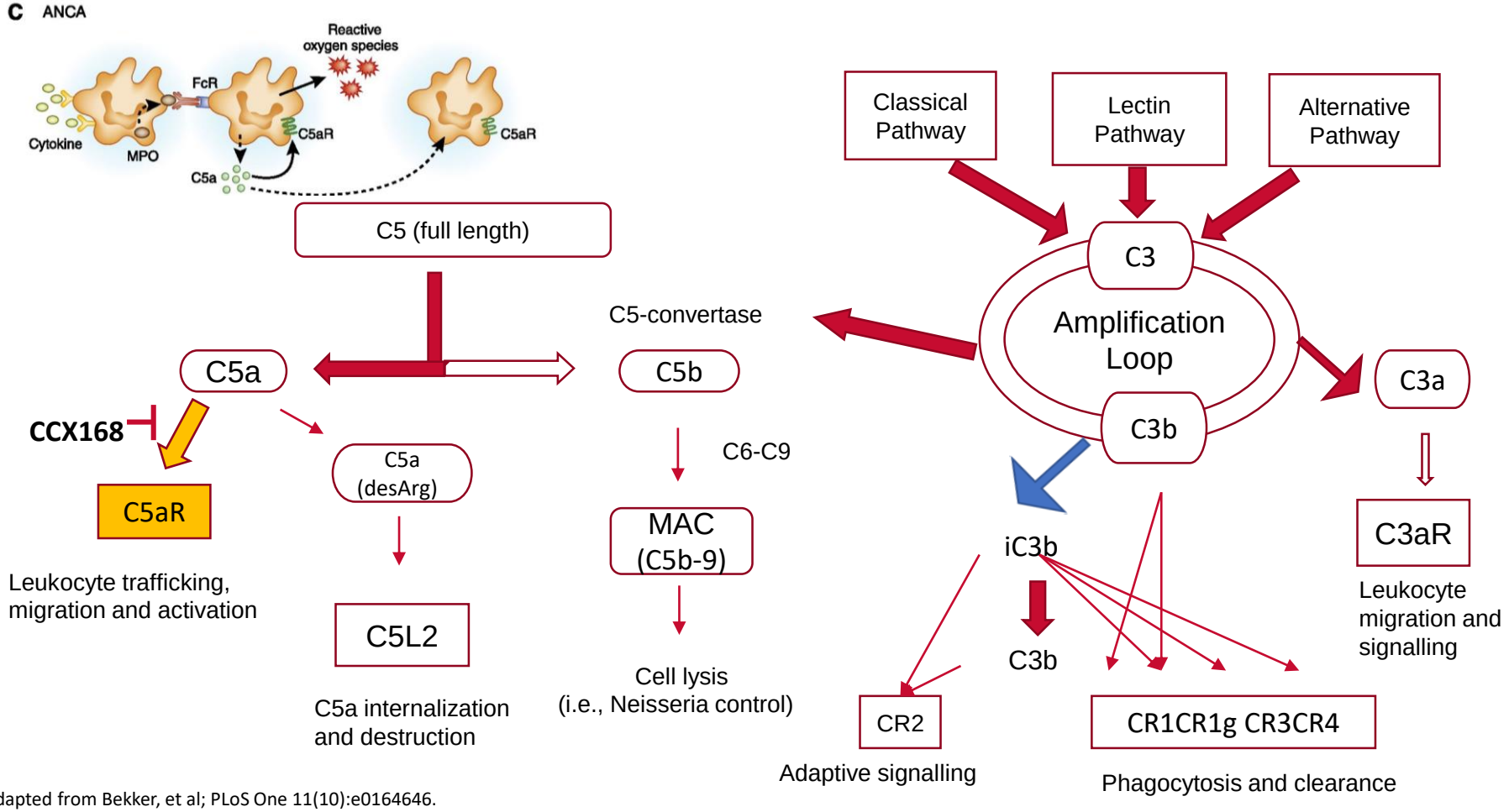




Su-Fang Chen et al. CJASN 2015;10:750-758

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

Mode of therapeutic action in AAV: C5aR inhibition By CCX168 will stop amplification of autoimmune neutrophil accumulation and activation at site of vascular inflammation



* Adapted from Bekker, et al; PLoS One 11(10):e0164646.

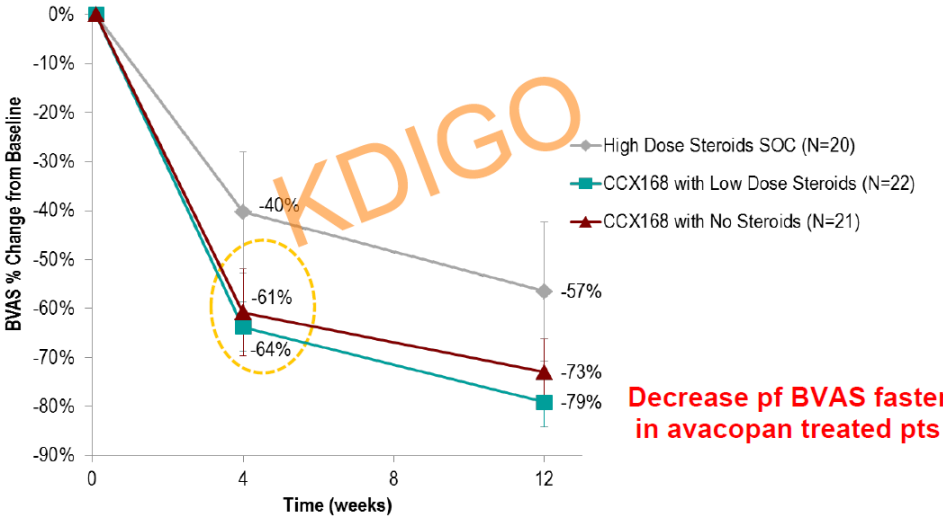
Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

67 pts with AAV randomized to:

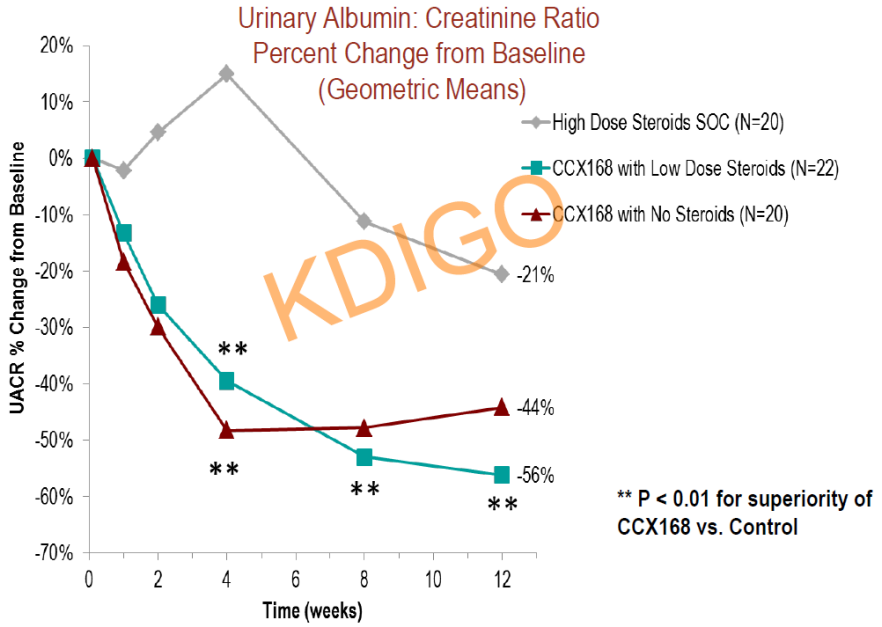
1) Standard of care (SOC) control: Placebo + CYC or RTX + full starting dose of prednisone (60 mg),

2) CCX168 30 mg b.i.d. + CYC or RTX + reduced starting dose of prednisone (20 mg), or

3) CCX168 30 mg b.i.d. + CYC or RTX + no prednisone.



Decrease pf BVAS faster in avacopan treated pts



** P < 0.01 for superiority of CCX168 vs. Control

Eculizumab in secondary atypical haemolytic uraemic syndrome

Table 3. aHUS associated with systemic disease

Patient	Age (years), gender	Systemic disease	Treatment before eculizumab	PE no. of sessions	Eculizumab (duration, no. of doses)	Time from aHUS to eculizumab (days)	Highest SCr (mg/dL) HD (Yes/No)	Latest SCr (mg/dL)	Follow-up (months)
16	51, female	SLE[a]	CS + Cyc + Rtx + PE	10	4 weeks, 4	31	4.2 Yes	Dialysis	0.9
17	16, female	SLE[a]	CS + MMF	–	10 weeks, 7	1	7.1 Yes	Dialysis	4.2
18	52, female	SLE	CS + Cyc + PE	27	2 weeks, 2	38	6.4 Yes	4.2	4.0
19	63, male	Scleroderma	CS + Cyc + PE	10	6 weeks, 5	55	4.9 No	Dialysis	12.9
20	56, male	Scleroderma	CS + Mtx + PE	10	8 weeks, 6	25	3.7 No	3.4	4.3
21	52, male	EGPA	CS + Cyc	–	16 weeks, 10	5	3.5 No	2.3	4.3
22	49, male	EGPA	CS + Cyc + PE	2	130 weeks, ongoing	15	6.5 Yes	Dialysis	29.5
23	38, male	Primary APS	–	–	14 weeks, 9	1	9.5 Yes	3.4	4.4

	Responders ($n = 20$)	Non-responders ($n = 9$)	P
Age (years)[a]	47.4 (35.9–57.5)	51.9 (49.9–60.1)	0.57
Gender, no. (%), male	11 (55.0)	5 (55.6)	1
Baseline SCr (mg/dL)[a]	3.4 (2.8–4.5)	3.4 (1.8–6.2)	0.75
SCr at the onset of Eculizumab (mg/dL)[a,b]	3.8 (3.2–5.4)	4.5 (3.4–6.7)	0.82
Dialysis, no. (%)[b]	9 (45)	5 (55.6)	0.70
Haemoglobin (g/dL)[a,b]	9.0 (8.1–10)	8.3 (7.7–104)	0.65
Platelet count (×1000/μL)[a,b]	78 (51–138)	61 (29–80)	0.25
Cause of aHUS, no. (%)			0.004
Systemic disease	2 (25)	6 (75)	
Drug induced	12 (80)	3 (20)	
Other causes	6 (100)	0 (0)	
Plasma exchange, no. (%)	17 (85)	7 (77.8)	0.50
Time between aHUS and eculizumab (days)[a]	9.5 (6–22.5)	25 (14–38)	0.059
Eculizumab duration (weeks)[a]	11.6 (4–24.7)	4.4 (3–8.4)	0.003

Cavero T et al. NDT 2017; 32:466-474

De novo thrombotic microangiopathy after kidney transplantation ☆

Neetika Garg [a,*,1], Helmut G. Rennke [b], Martha Pavlakis [a], Kambiz Zandi-Nejad [a]

Classification of post-transplant TMA.

1. Recurrent TMA after transplantation
   - Atypical hemolytic uremic syndrome
   - Thrombotic thrombocytopenic purpura
   - Autoimmune disorders and glomerulonephritis with previously documented TMA in native kidneys e.g. scleroderma and systemic lupus erythematosus, with or without anti-phospholipid antibodies
2. De novo TMA after transplantation
   - Immunosuppressive medication associated – TMA: Calcineurin inhibitor or mammalian target of rapamycin inhibitor or combination of the two
   - Antibody-mediated rejection associated TMA
   - Genetic, associated with complement regulatory gene abnormalities
   - Medication related e.g. anti-vascular endothelial growth factor inhibitors
   - Viral infections, e.g. hepatitis C, cytomegalovirus, parvovirus and BK
   - C3 glomerulopathies as cause of ESRD, where phenotypical shift to aHUS after transplantation can occur
   - Recurrent TMA, where a native kidney biopsy is not pursued and TMA as cause of ESRD is not established

Table 2. Drug-induced aHUS

Patient	Age (years), gender	Offending drug	Treatment before eculizumab	PE no. of sessions	Eculizumab (duration, no. of doses)	Time from aHUS to eculizumab (days)	Highest SCr (mg/dL) HD (Yes/No)	Latest SCr (mg/dL)	Follow-up (months)
1	43, female	Tacrolimus[a]	DW + PE	3	2 weeks, 2	4	3.8 No	1.1	16.2
2	63 female	Tacrolimus[a]	DW + PE	10	18 weeks, 11	53	3.1 Yes	2.0	5.9
3	34, male	Tacrolimus[a]	PE	3	24 weeks, 14	10	9.8 Yes	2.6	6.7
4	18, female	Tacrolimus[a]	DW + PE	2	3 weeks, 3	14	2.1 No	2	9.6
5	52, female	Tacrolimus[a]	DW	–	8 weeks, 6	26	2.9 No	1.2	8.3
6	43, male	Tacrolimus[a]	DW + PE	6	30 weeks, 17	35	3.8 Yes	1.1	16.2
7	36, female	Everolimus[a]	DW + PE	6	6 weeks, 5	9	4.2 No	2.1	17.5
8	60, male	Tacrolimus[b]	DW	–	4 weeks, 4	53	3.4 Yes	2.5	3.4
9	67, male	Tacrolimus, everolimus[b]	DW + PE	6	6 weeks, 5	10	1.8 No	2.0	1.7
10	59, male	Tacrolimus, everolimus[b]	DW + PE	5	10 weeks, 7	7	3.5 No	2.0	4.8
11	65, male	Tacrolimus, everolimus[b]	DW + PE	6	2 weeks, 2	9	3.3 No	2.4	4.5
12	51, male	Tacrolimus[c]	DW + PE	2	4 weeks, 4	10	2.4 No	0.6	2.9
13	54, female	Tacrolimus, sirolimus[c]	DW + PE	7	3 weeks, 3	7	4.2 Yes	1.2	1.5
14	55, male	Tacrolimus[d]	DW + PE	12	18 weeks, 11	27	3.0 No	2.4	14.1
15	42, female	Tacrolimus[e]	DW + PE	3	3 weeks, 3	13	1.4 No	0.5	17.0

	Responders ($n = 20$)	Non-responders ($n = 9$)	P
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Cavero T et al. NDT 2017; 32:466-474

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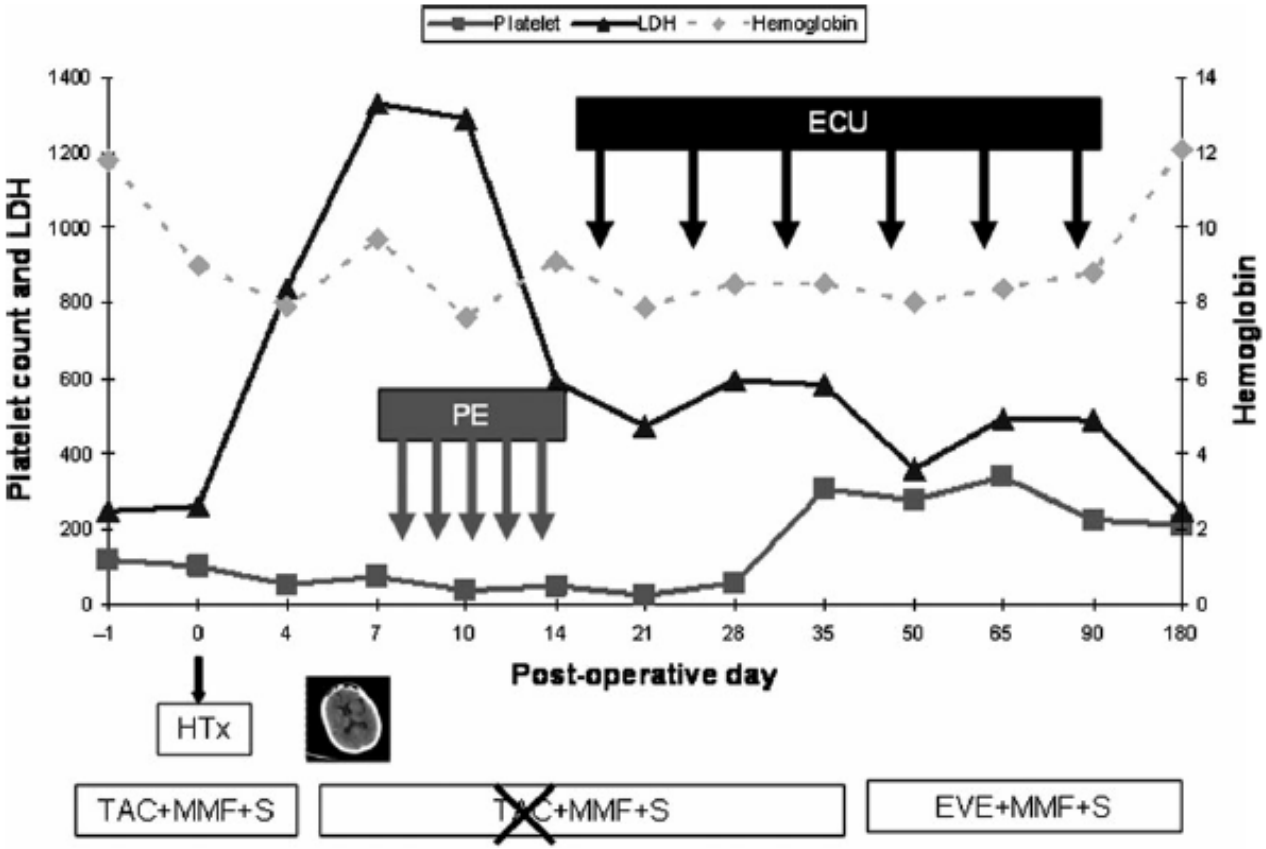
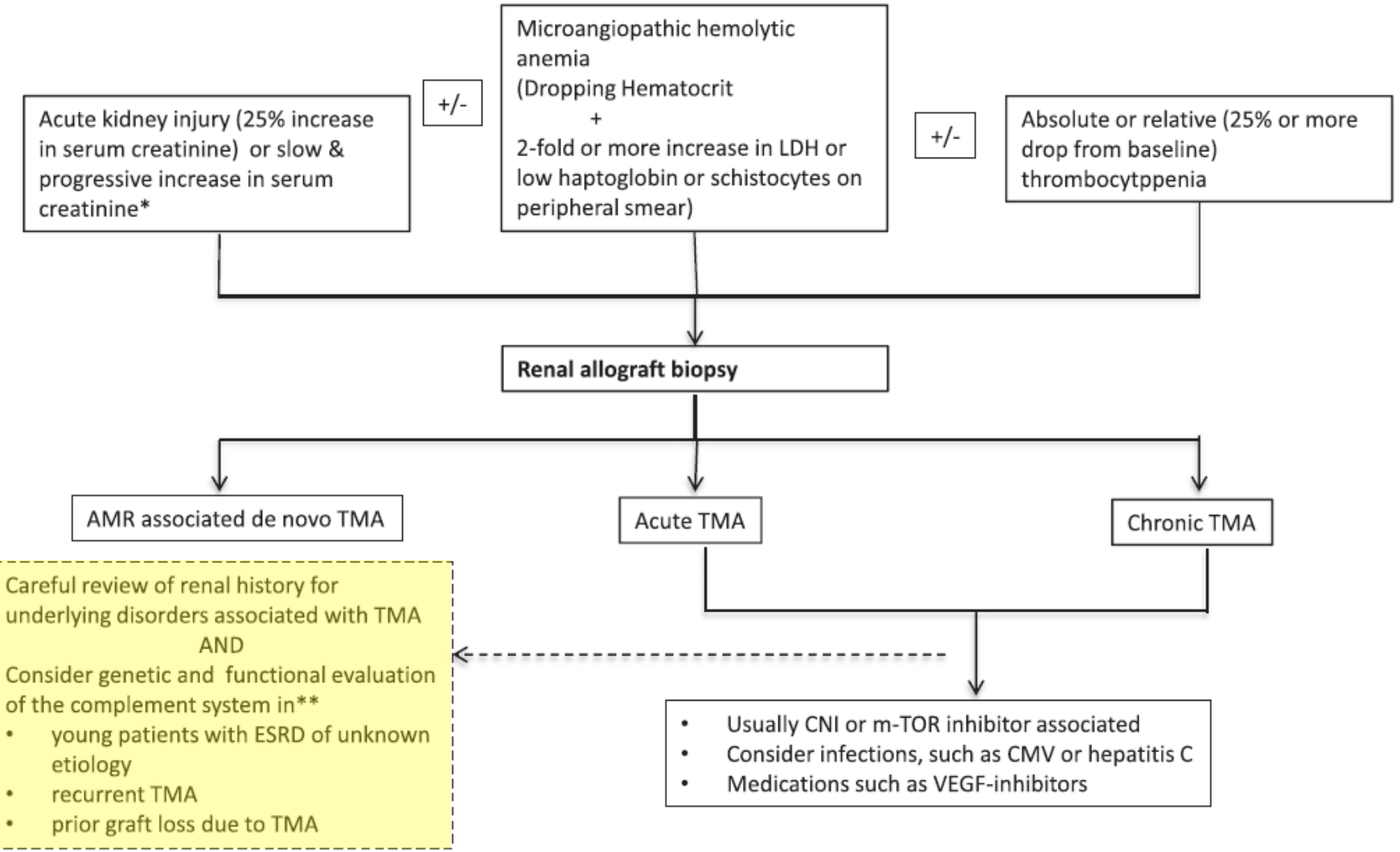
LETTER TO THE EDITORS

A case of thrombotic micro-angiopathy after heart transplantation successfully treated with eculizumab



Abbreviations: ECU, eculizumab; EVE, everolimus; HTx, heart transplantation; MMF, mycophenolate mofetil; PE, plasma exchange; S, steroids; TAC, tacrolimus.

Enrique Morales, Cristina Rabasco, Eduardo Gutierrez and Manuel Praga



* Post-transplant de novo TMA frequently presents without any evidence of microangiopathic anemia or thrombocytopenia. Biopsy should be considered for acute kidney injury or slow progressive increase in serum creatinine in absence of another apparent cause.
** While current evidence does not support evaluation of the complement system in all patients with de novo TMA, we recommend pursuing this in individuals where the diagnosis of aHUS may have been missed as the cause of ESRD, e.g. young patients where cause of ESRD is not known, those with recurrent TMA or those with history of prior graft losses from TMA.

Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities

Kidney International (2017)

Table 1 | Baseline clinical features and laboratory evaluation

Patient No.	Age (yr)	Sex	BP (mm Hg)	SCr (μmol/l)	uProt (g/d)	uRBC	ESRD	Hb (mmol/l)	LDH (U/l)	MAHA[a]	Platelets ($\times 10^9$/l)[b]
1	38.4	F	184/140	1730	NA	NA	Y	5.1	1800	Y	224
2	40.3	M	205/114	1195	2.3	Y	Y	5.7	1104	Y	158
3	37.7	M	200/120	586	3.9	Y	Y	5.3	2125	Y	100
4	32.0	F	180/120	1138	NA	NA	Y	5.9	1486	Y	142
5	65.0	M	195/105	162	1.5	Y	N	7.9	271	N	98
6	41.1	F	180/120	334	0.7	Y	Y	7.5	291	N	285
7	28.5	F	224/122	1065	1.6	Y	Y	5.1	298	N	228
8	27.9	M	240/150	673	1.6	Y	Y	7.9	165	N	133
9	44.0	F	220/120	649	0.4	Y	Y	8.2	339	N	340

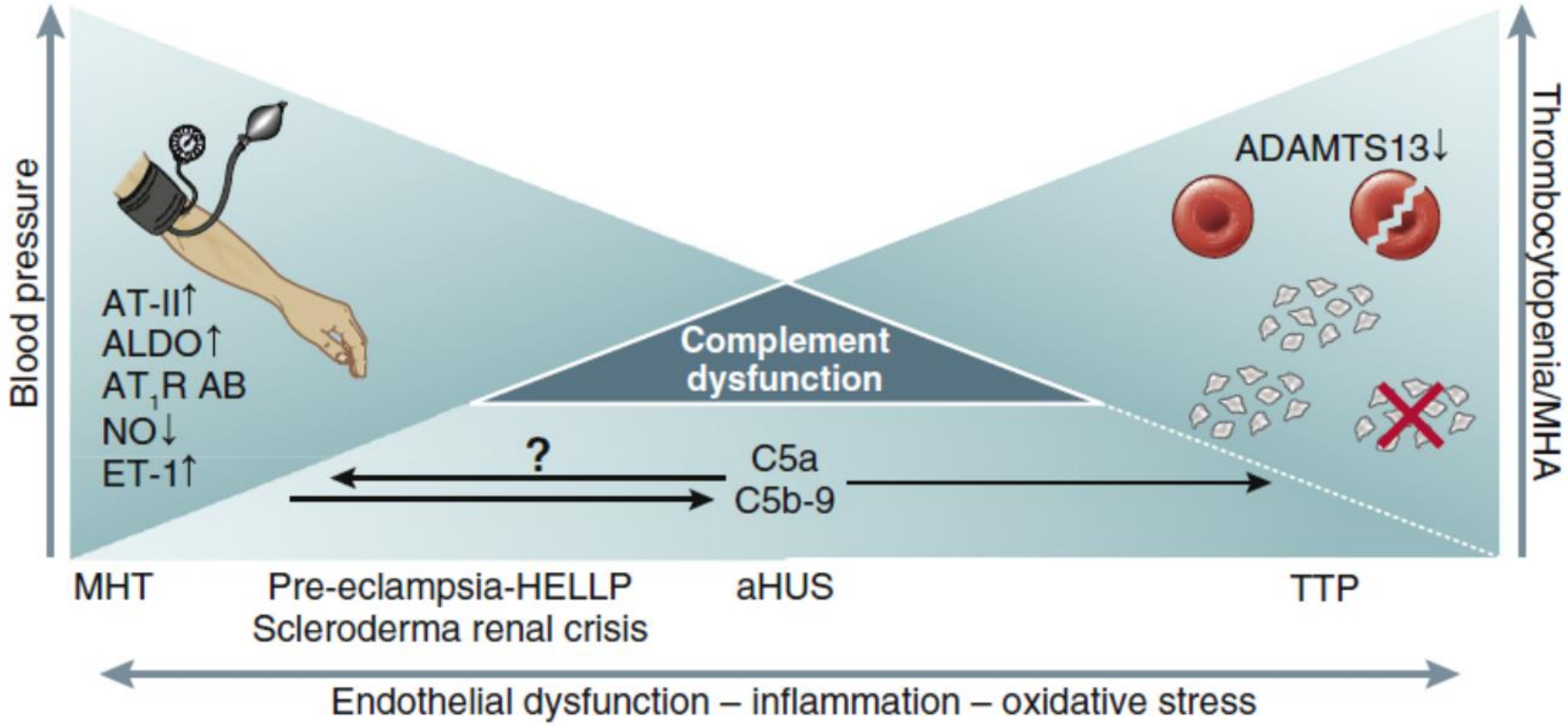
Table 2 | Complement abnormalities **67% genetic defects**

Patient No.	Mutation(s)	*CFH*-H3[11]	FHAA	CP (%)[a]	AP (%)[b]	sC5b-9 (ng/ml)[c]
1	*C3*-R161W[18]	N	Negative	95	64	2800
2	*CD46*-ΔD237/S238,[15] *CFH*-Q950H[11]	Y	Negative	97	107	1000
3	*C3*-R161W[18]	Y	ND	94	97	640
4	*CFH*-C853R[16]	Y	ND	104	71	1840
5	No mutations	N	ND	99	99	1800
6	*CFI*-N151S[14]	N	ND	97	87	4200
7	*C3*-R161W,[18] Δ*CFHR1-CFHR3*[d]	N	Negative	110	62	1840
8	No mutations	Y	Negative	90	74	440
9	No mutations	N	Negative	113	110	3800

At the time of presentation, a clinical diagnosis of **malignant nephrosclerosis** was clinically inferred. In all patients, mild-to-moderate hypertensive retinopathy was found, and papilledema was observed in 1 case (no. 8). Indeed, **7 patients had a known medical history of hypertension**, including 2 patients with documented episodes of preeclampsia (nos. 1, 7) and/or malignant hypertension (no. 7).

Severe hypertension with renal thrombotic microangiopathy: what happened to the usual suspect?

Steven Van Laecke[1] and Wim Van Biesen[1]



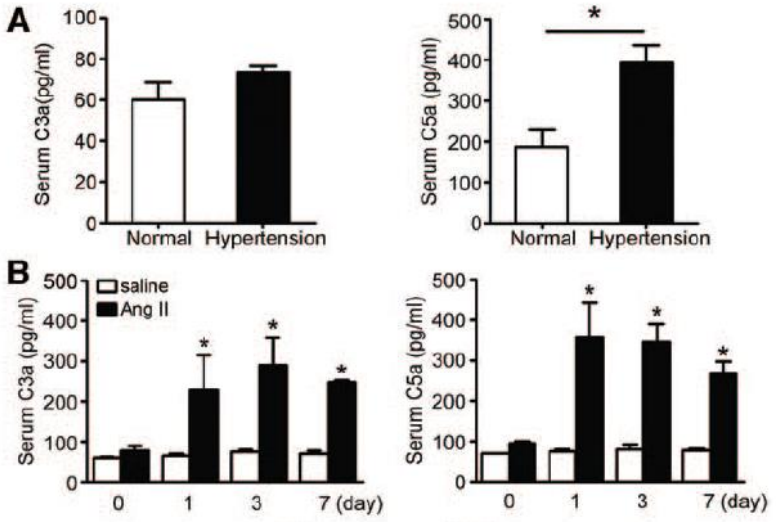
Endotheliopathies!!

Kidney International (2017) **91,** 1271–1274;

Anaphylotoxins in hypertension

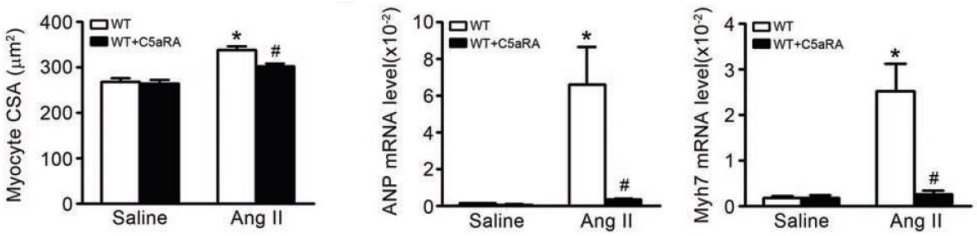
Complement 5a Receptor Mediates Angiotensin II–Induced Cardiac Inflammation and Remodeling

Congcong Zhang, Yulin Li, Chunxiao Wang, Yina Wu, Wei Cui, Takashi Miwa, Sayaka Sato, Huihua Li, Wen-Chao Song, Jie Du



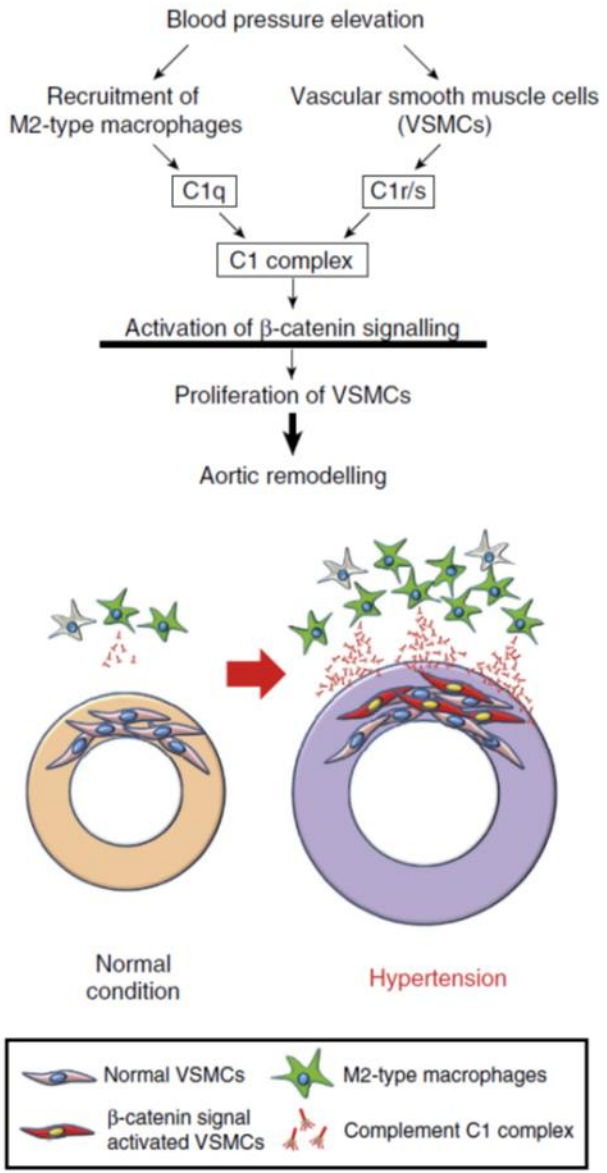
(*Arterioscler Thromb Vasc Biol.* 2014;34:1240-1248.)

Antagonist of C5aR Prevents Cardiac Remodeling in Angiotensin II–Induced Hypertension

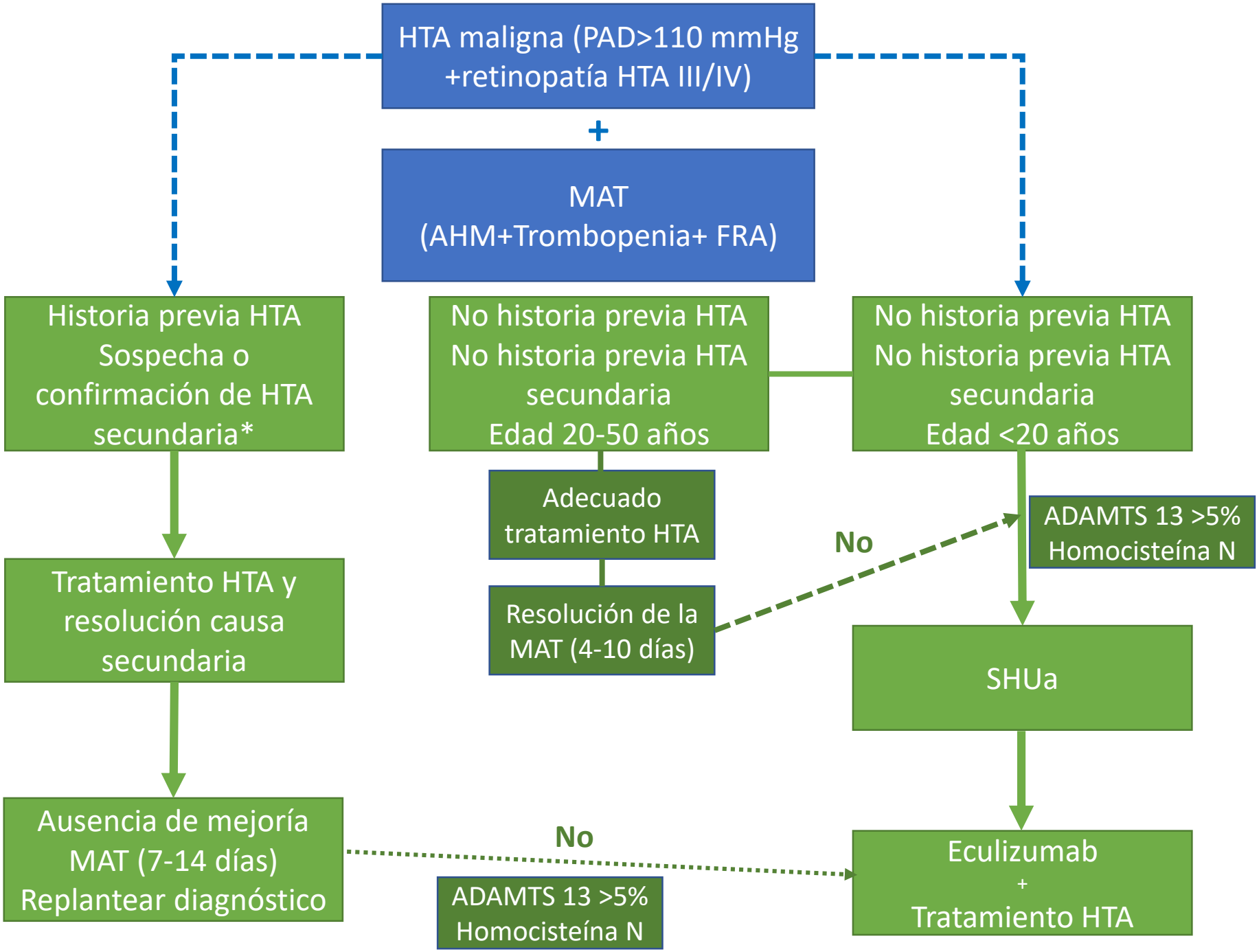


American Journal of Hypertension 27(6) June 2014

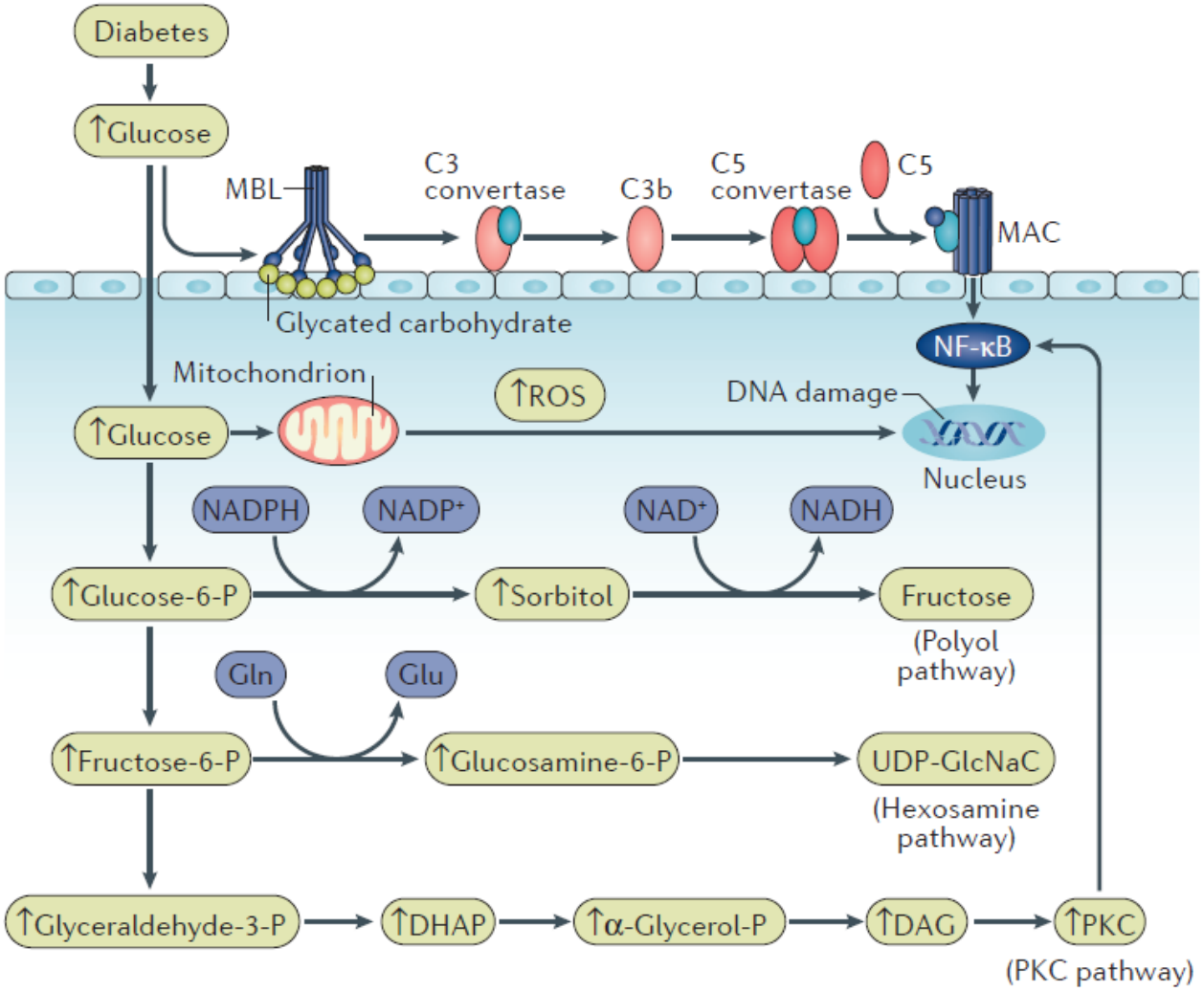
Complement C1q-induced activation of β-catenin signalling causes hypertensive arterial remodelling



NATURE COMMUNICATIONS | 6:6241 | DOI: 10.1038/

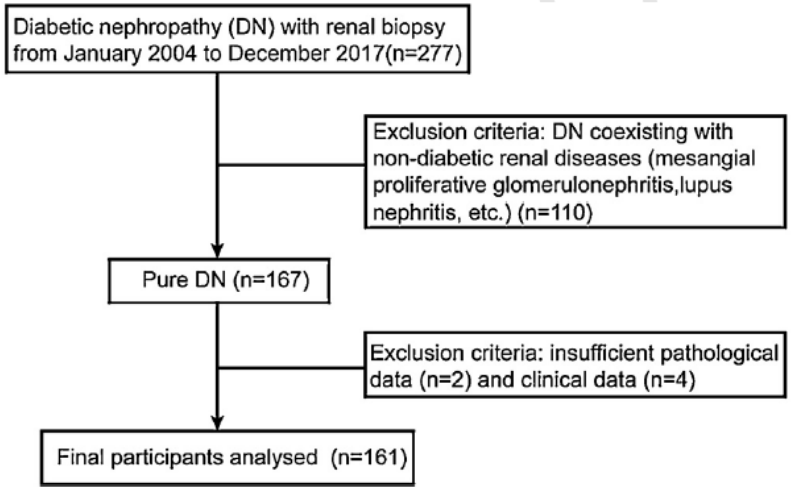

HTA maligna (PAD>110 mmHg +retinopatía HTA III/IV)
+
MAT (AHM+Trombopenia+ FRA)
Historia previa HTA Sospecha o confirmación de HTA secundaria*
No historia previa HTA No historia previa HTA secundaria Edad 20-50 años
No historia previa HTA No historia previa HTA secundaria Edad <20 años
Adecuado tratamiento HTA
Resolución de la MAT (4-10 días)
No
ADAMTS 13 >5% Homocisteína N
Tratamiento HTA y resolución causa secundaria
SHUa
Ausencia de mejoría MAT (7-14 días) Replantear diagnóstico
No
ADAMTS 13 >5% Homocisteína N
Eculizumab + Tratamiento HTA

The role of the complement system in diabetic nephropathy



Nat Rev Nephrol 2017; 13(5):311-318

Complement deposition on renal histopathology of patients with diabetic nephropathy



In conclusion, deposition of C1q and C3c on renal histopathology evaluation was associated with more severe kidney damage in DM patients with DN. Nevertheless, further investigations are still needed to determine the precise role of complement in the development of DN

Table 3
Characteristics of patients according to C3c and/or C1q deposition.

Variables	Both C3c and C1q deposition	Only C1q deposition	Only C3c deposition	No C3c and C1q deposition
n (%)	38 (23.6)	6 (3.7)	51 (31.7)	66 (41.0)
Clinical characteristics				
Serum creatinine (μmol/L)[b]	219.95 (161.30–417.00)	151.35 (129.20–214.50)	181.50 (99.00–264.10)	126.92 (9660–194.20)
Urinary protein (g/24 h)[b]	7.04 ± 4.15	8.85 ± 4.70	5.29 ± 3.79	4.74 ± 3.75
eGFR (mL/min/1.73 m^2)[b,c]	32.09 ± 24.21	47.31 ± 29.76	46.06 ± 29.31	55.14 ± 32.87
Pathological characteristics				
Glomerular class (I/IIa/IIb/III/IV)	0/5/23/9/1	0/0/5/0/1	0/8/28/5/10	1/7/46/3/9
IFTA Score (0/1/2/3)[b]	0/3/27/8	0/1/4/1	2/13/32/4	4/22/37/3
Interstitial inflammation Score (0/1/2)	0/9/29	0/2/4	1/19/31	7/22/37
Vascular lesion Score (0/1/2)	5/19/14	1/1/4	16/18/17	24/25/17
Global sclerosis (%)[a]	30.0% ± 21.0%	26.0% ± 29.0%	30.0% ± 21.0%	20% ± 18%

Diabetes Metab. 2018 Sep 19

Patient and target selection

- As **complement therapeutics** have been approved for the treatment of kidney diseases, awareness of the role of complement in these diseases has increased among **nephrologists.**
- As the number of **candidate drugs** in clinical pipelines increases, the choice of the **appropriate target** and corresponding drug will become ever more important.
- **Identifying biomarkers or genetic profiles** for selecting patients to be enrolled in clinical trials will become increasingly important.

All Things

omplement