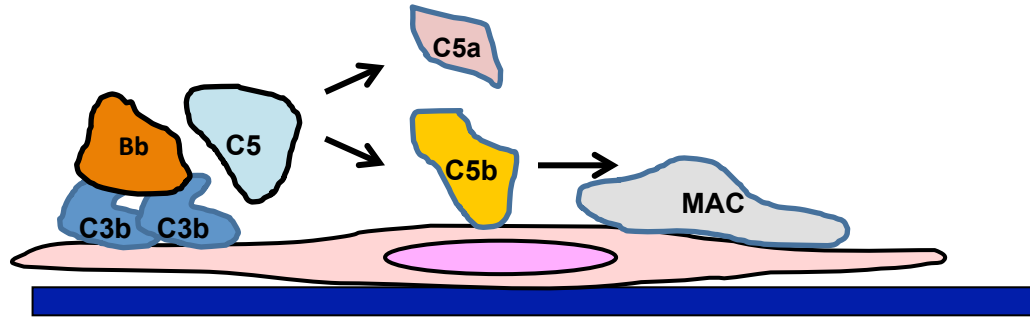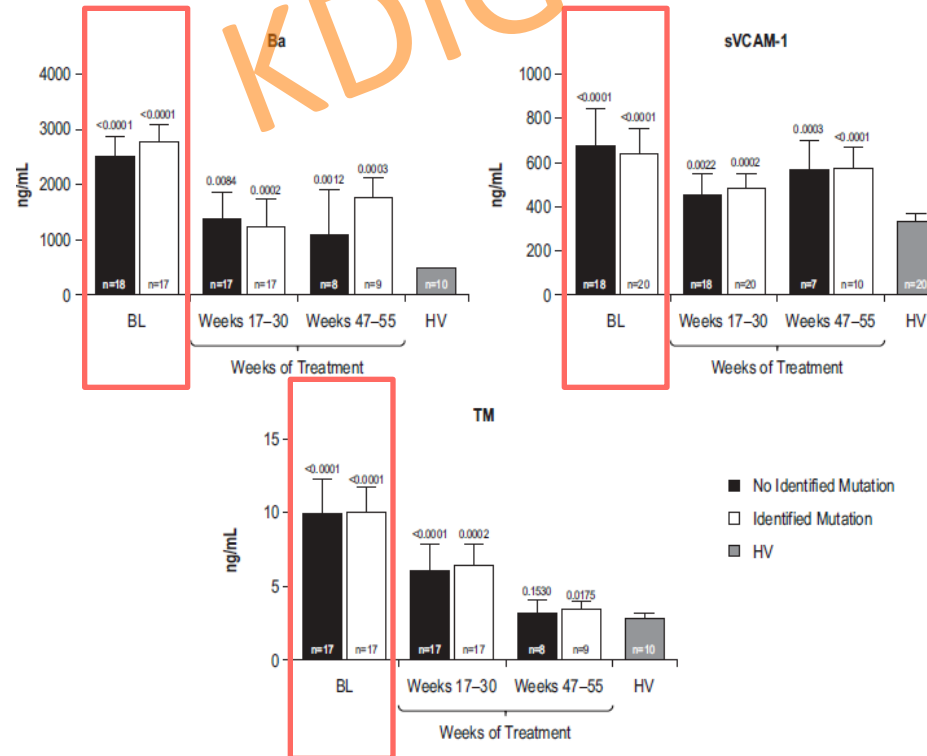# Issues in the treatment of aHUS

Plasma therapy fails to curb complement activation and EC damage and improve renal function.

Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS

Roxanne Cofiell, Anjli Kukreja, Krystin Bedard, Yan Yan, Angela P. Mickle, Masayo Ogawa, Camille L. Bedrosian and Susan J. Faas
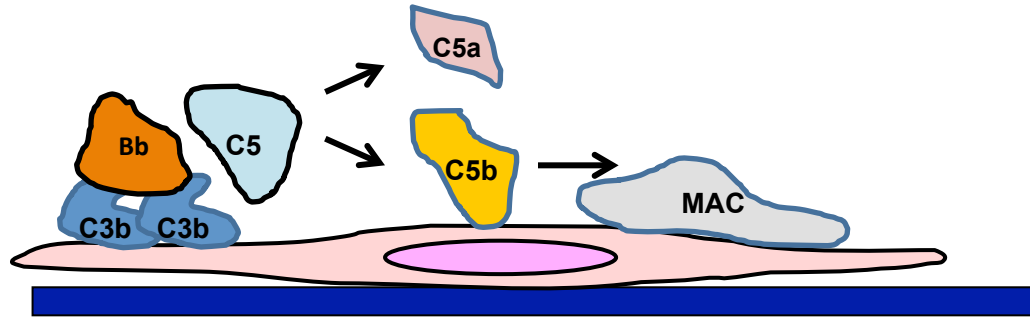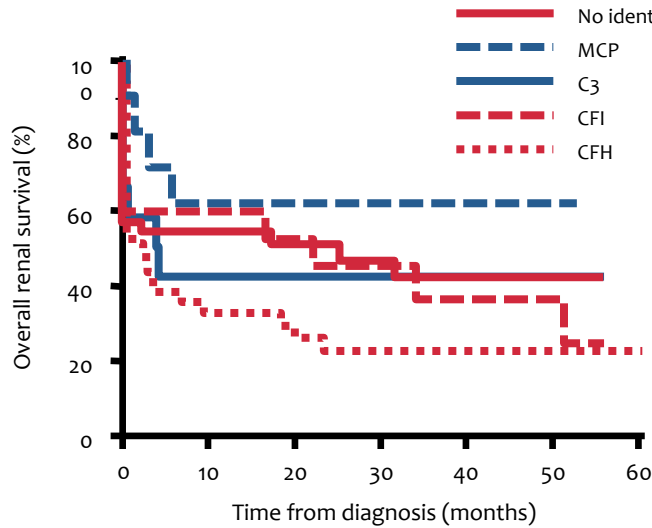
Issues in the treatment of aHUS

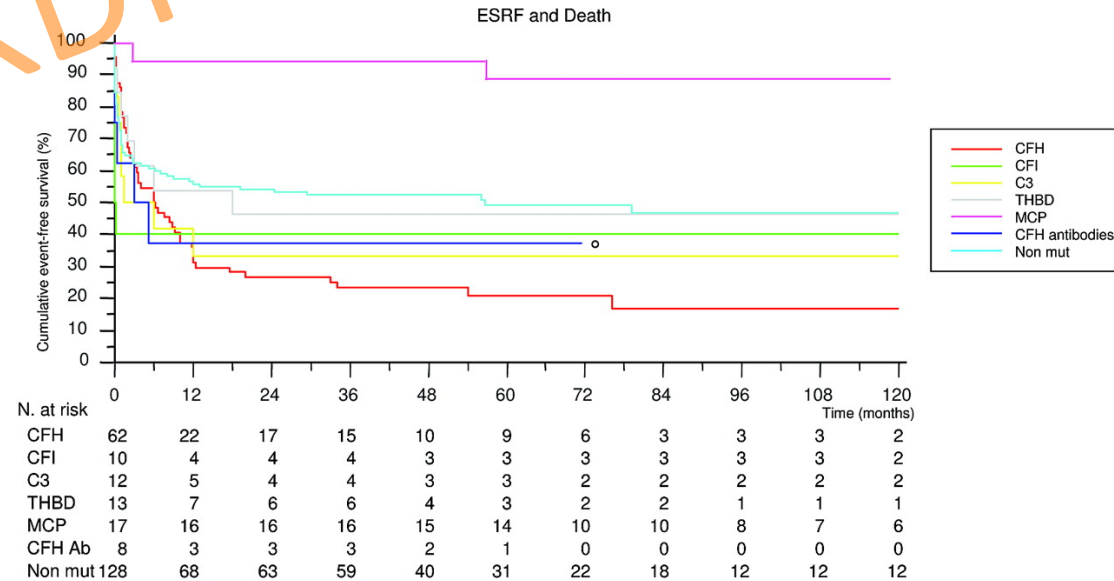**Plasma therapy fails to curb complement activation and EC damage and improve renal function.**
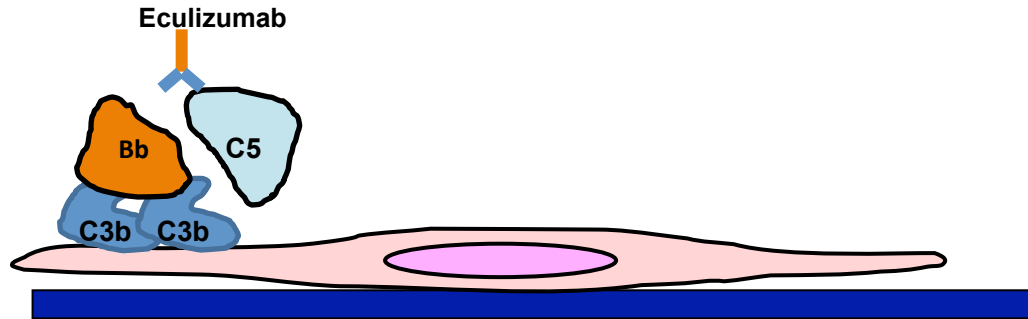
V Frémeaux-Bacchi et al. CJASN 2013

Marina Noris et al. CJASN 2010

65% of patients were treated with plasma exchange / plasma infusion

68% of patients were treated with plasma exchange / plasma infusion

Issues in the treatment of aHUS

Eculizumab inhibits complement activation and EC damage and improves renal function.
(prospective non controlled trials)

Adults

Follow-up	ESRD (% patients)			
	French cohort **N= 125**	**Trial 1** **N=17**	**Trial 2** **N=20**	**Trial 4** **N=41**
First episode	46%			
6 months		6%	10%	15%
1 year	56%	6%	10%	12%
2 years		12%	10%	
5 years	64%			

C. Loirat
Ped Nephrol, 2015

French cohort: Fremeaux-Bacchi *et al*, CJASN 2013

Issues in the treatment of aHUS
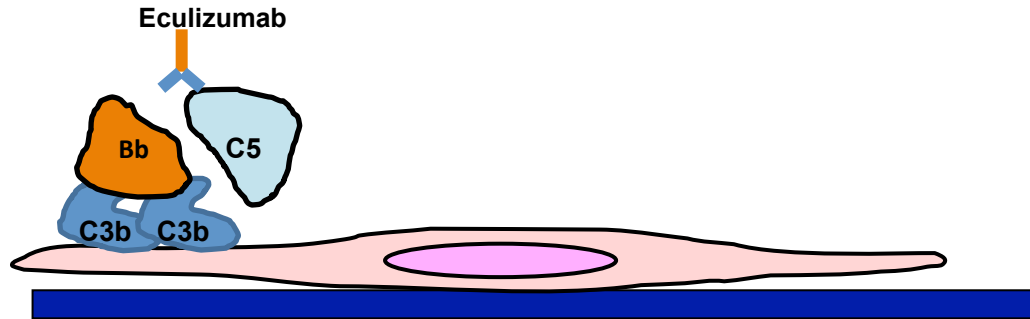
Eculizumab inhibits complement activation and EC damage and improves renal function.
(retrospective studies)

	(2004-2008) Historical controls (n=41)	Eculizumab-treated aHUS cases (n=18)*	p-value
Female	28 (68%)	13 (72%)	0.8
Age	34 (18-85)	27 (19-53)	0.4
Complement genes mutations	28 (68%)**	13 (72%)	0.2
Hemodialysis	29 (71%)	12 (63%)	0.8
Platelet count > 150 G/L	6/36 (17%)	4 (21%)	0.6
Plasma exchanges	24/38 (63%)***	15 (83%)	0.1
End-stage renal disease within 3m of aHUS flare	20 (46%)	3 (17%)	0.02
End-stage renal disease at 1 year	23/36 (63%)	2/8 (25%)	0.04

Fakhouri F et al. Am J Kidney Dis 2014
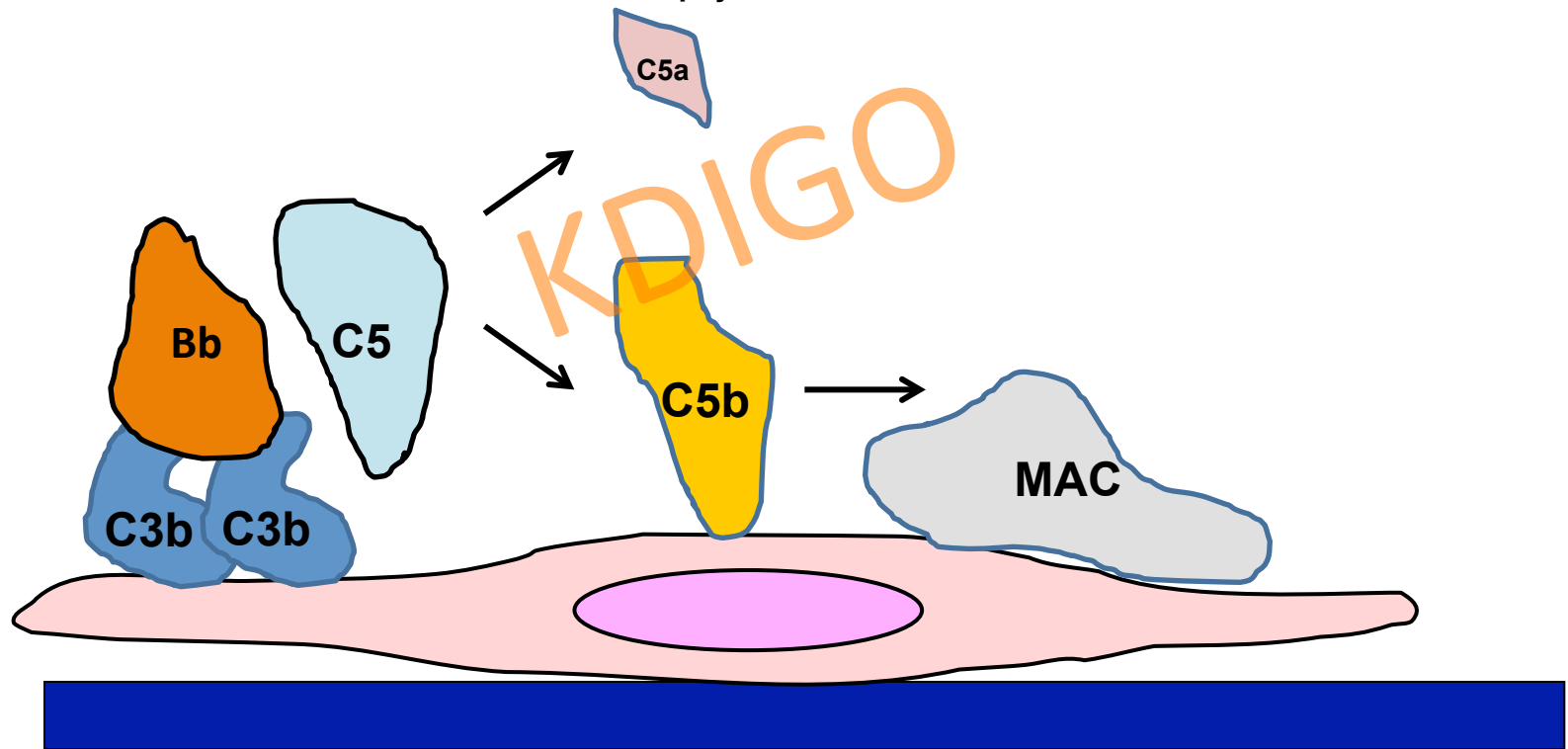
Issues in the treatment of aHUS

Why does a minority of patients not respond to Ecu?
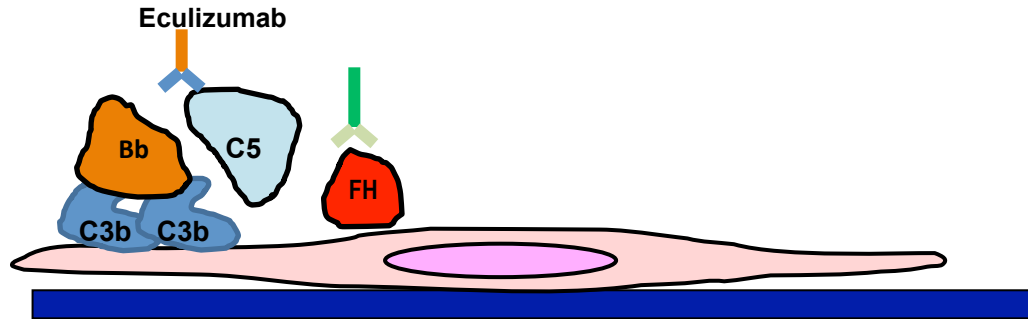**How to monitor complement blockade** (CH50, AP50, free vs total C5, EC tests)**?**
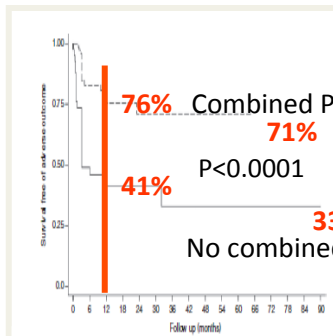**sC5b-9 may remain detectable…**
Other therapeutic options?
Prophylaxis?

Issues in the treatment of aHUS

Eculizumab

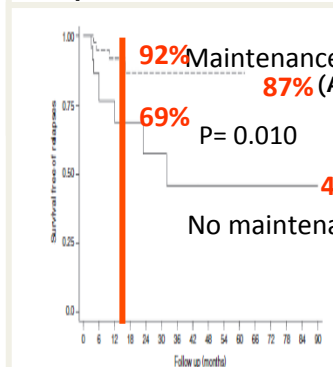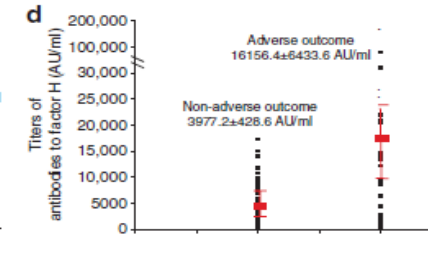**What is the best strategy for aHUS due to anti-FH antibodies?**

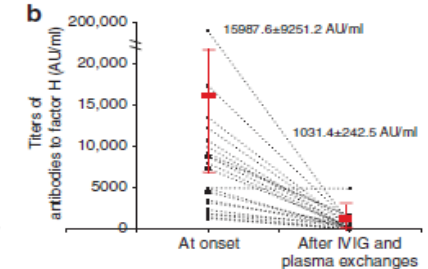**PE + Immunosupressive therapies ± eculizumab (or vice-versa)?**

76% Combined PE+IS
71%
P<0.0001
41%
33%
No combined therapy

Relapse-free survival

92% Maintenance IS
87% (AZA or MMF)
69%
P= 0.010
46%
No maintenance IS
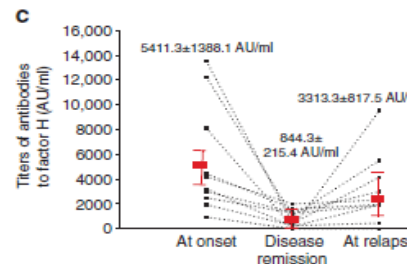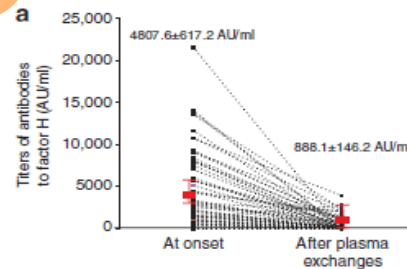
Monitoring of anti-CFH Ab should guide treatment tapering

Sinha, KI 2013

Issues in the treatment of aHUS

What pathophysiological model apply to secondary HUS?

Issues in the treatment of aHUS
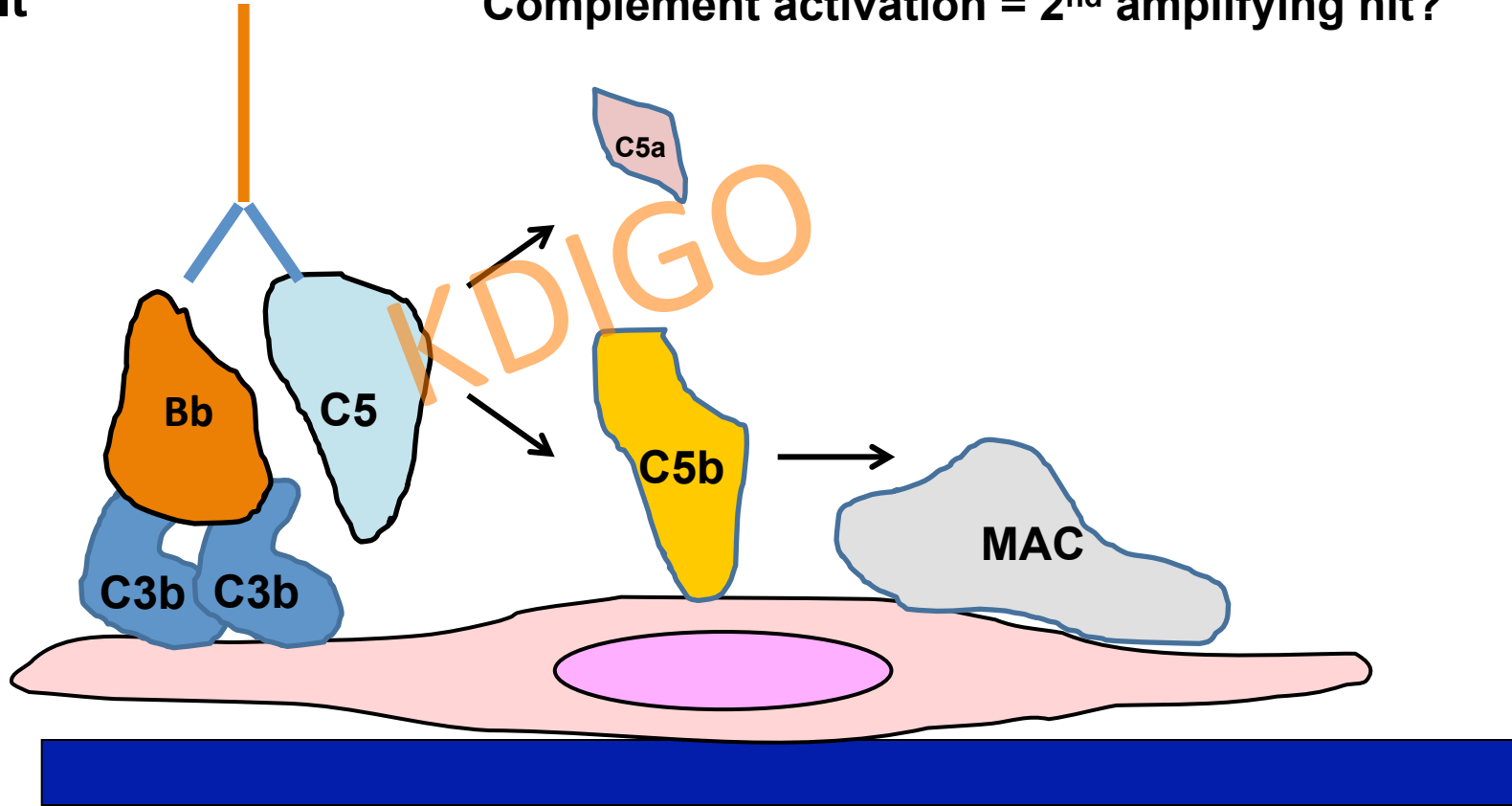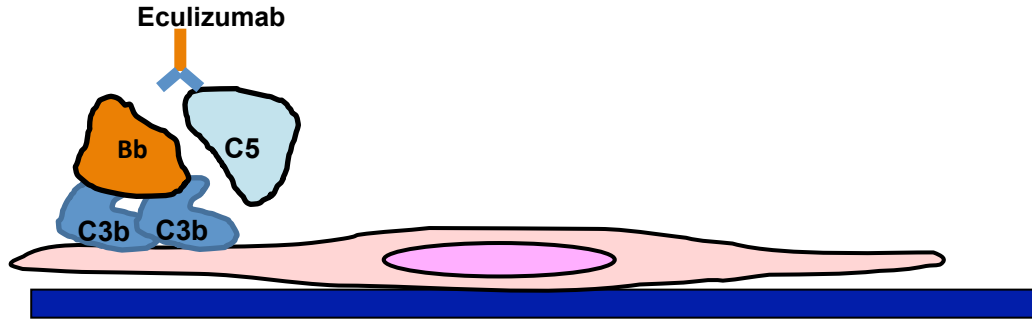
For how long should we use eculizumab in aHUS patients?

Does chronic « clinically-relevant » complement activation occur in all aHUS patients?

Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS

Roxanne Cofiell, Anjli Kukreja, Krystin Bedard, Yan Yan, Angela P. Mickle, Masayo Ogawa, Camille L. Bedrosian, and Susan J. Faas

Issues in the treatment of aHUS
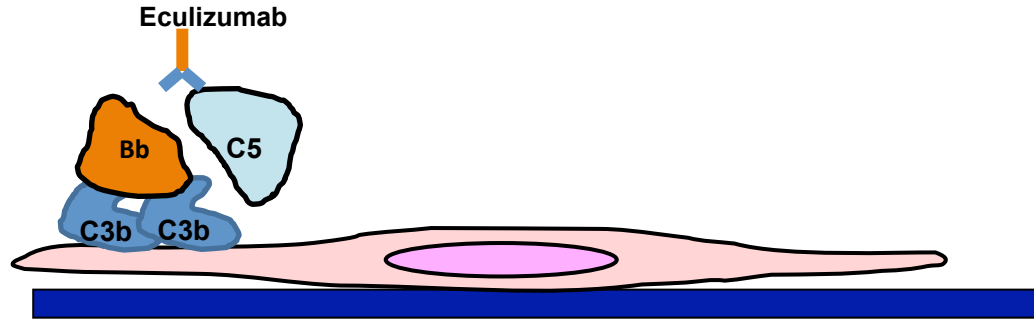
For how long should we use eculizumab in aHUS patients?

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Risk of relapse / CKD-ESRD vs Meningococcal infection / biweekly perfusions / cost.

Issues in the treatment of aHUS

(Menne, ASN 2015)

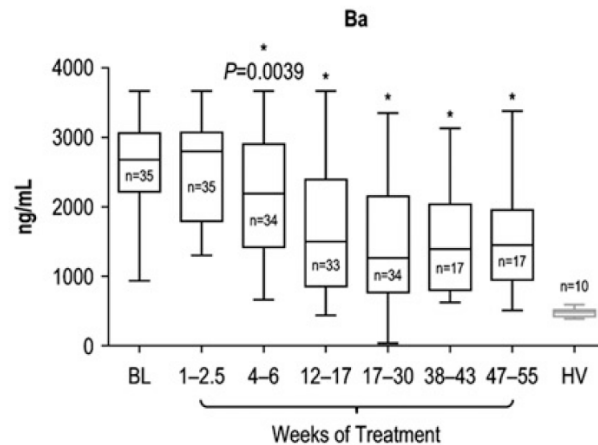# Issues in the treatment of aHUS

Eculizumab

Bb   C5

C3b   C3b

For how long should we use eculizumab in aHUS patients?

Does chronic « clinically-relevant » complement activation occur in all aHUS patients?

Risk of relapse / CKD-ESRD vs Meningococal infection / biweekly perfusions / cost.

Can eculizumab be discontinued in some patients
and how to select candidates for eculizumab withdrawal?

Age
Quality of renal recovery
Duration of Ecu treatment
Native kidneys vs renal graft
Willingness of the patient (physician)
Biomarkers C activation / EC damage

Issues in the treatment of aHUS

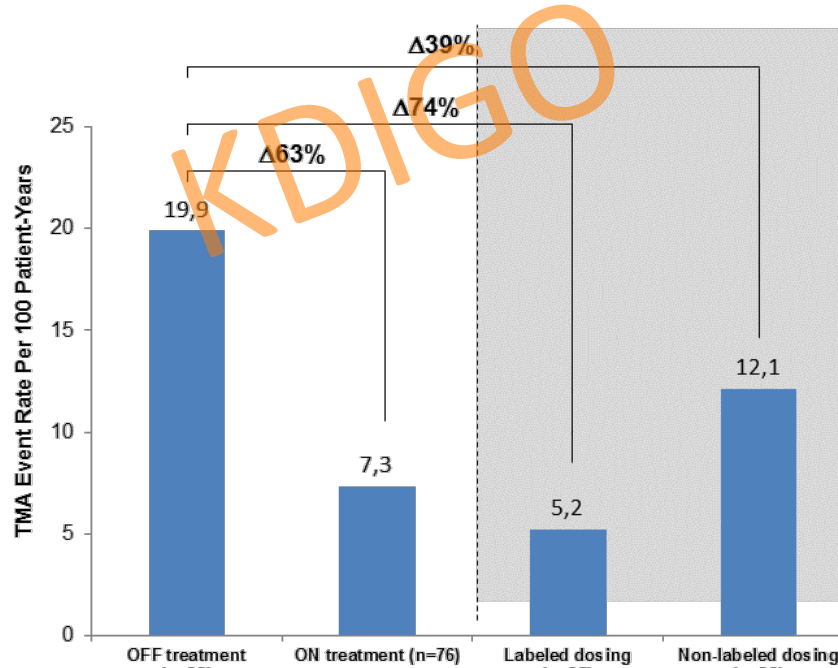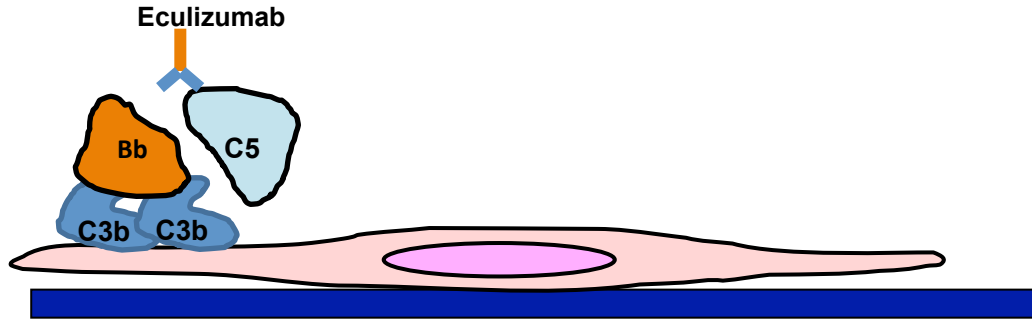

For how long should we use eculizumab in aHUS patients?

Does chronic « clinically-relevant » complement activation occur in all aHUS patients?

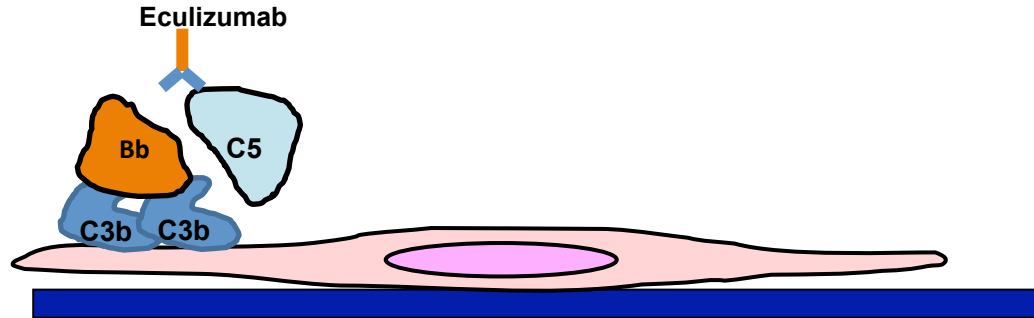**Risk of relapse / CKD-ESRD vs Meningococal infection / biweekly perfusions / cost.**

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Age
Quality of renal recovery
Duration of Ecu treatment
Native kidneys vs renal graft
Willingness of the patient (physician)
Biomarkers C activation / EC damage
Complement genetics

Issues in the treatment of aHUS

Eculizumab

Bb   C5

C3b   C3b
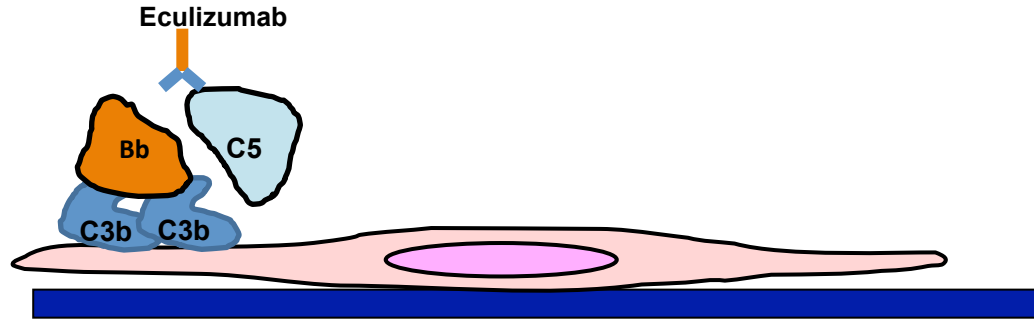
For how long should we use eculizumab in aHUS patients?

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome: A Report of 10 Cases

Ardissino, AJKD 2013

KDIGO

Table 1. Patients' Baseline Characteristics and Biomarkers of TMA Activity Before Eculizumab Discontinuation and at Last Available Observation

Patient No.	Age at aHUS Onset (y)	Sex	Complement Abnormality[a]	Relapse	Time Since Start of Eculizumab (mo)	Duration of Eculizumab Discontinuation (mo)	Scr (eGFR[b])		Platelet Count (10³/μL)		LDH (IU/L)		Haptoglobin (mg/dL)		UPCR (mg/mg)	
							T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
1	4.3	M	CFH (p.Ser1191Leu)	Yes	31.0	1.5	0.92 (49)	0.80 (58)	334	290	367	206	97	103	0.67	0.17
2	37.7	F	CFH (p.Arg1210Cys) + CFI (p.Asp519Asn) + THBD (p.Ala43Thr)	Yes	25.2	0.9	1.41 (44)	1.25 (51)	244	227	482	219	117	94	1.53	0.96
3	52.7	M	CFI (p.Ile140Thr)	No	24.3	22.7	1.03 (97)	1.00 (100)	180	256	467	371	312	292	NA	0.08
4	34.8	F	CFI (p.Gly269Ser)	No	21.5	10.1	2.72 (29)	2.54 (22)	281	286	406	403	98	88	1.38	0.70
5	2.6	M	CFI (p.Asp519Asn)	No	21.4	15.9	0.38 (132)	0.44 (117)	261	299	517	426	68	105	0.35	0.24
6	1.3	F	Homozygous deletion at *CFHR3/R1* locus	No	19.9	6.5	0.29 (128)	0.27 (138)	447	390	688	654	91	60	3.46	2.32
7[c]	19.1	M	Anti-CFH antibody (titer, 27 IU)	No	19.8	14.2	1.33 (72)	1.20 (79)	245	167	390	325	236	178	0.14	0.08
8	5.4	F	MCP (p.Phe175Val)	No	14.0	13.5	1.28 (36)	0.52 (89)	300	420	682	423	46	78	3.21	0.20
9	13.3	M	Anti-CFH antibody (titer, 100 IU) + homozygous deletion at *CFHR3/R1* locus	No	11.2	8.6	0.64 (110)	0.58 (122)	268	298	435	371	108	106	0.22	0.19
10	10.9	F	CFH (p.Gln950His) + homozygous deletion at *CFHR3/R1* locus + anti-CFH antibody (titer, 230 IU)	Yes	6.4	1.2	0.95 (73)	0.66 (105)	180	239	466	221	88	88	0.45	0.12

Issues in the treatment of aHUS

For how long should we use eculizumab in aHUS patients?

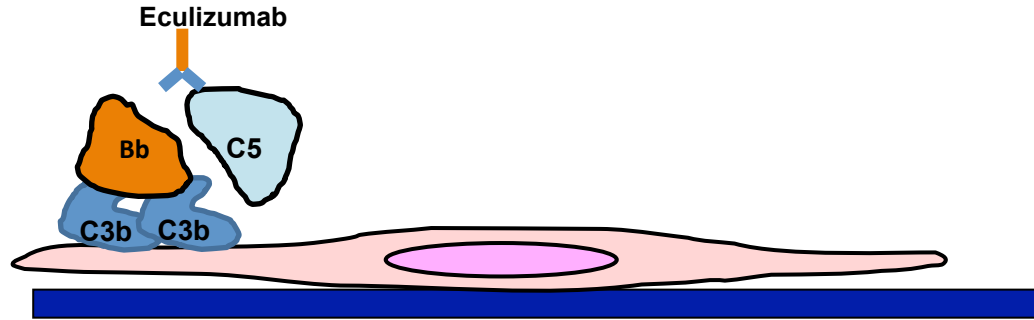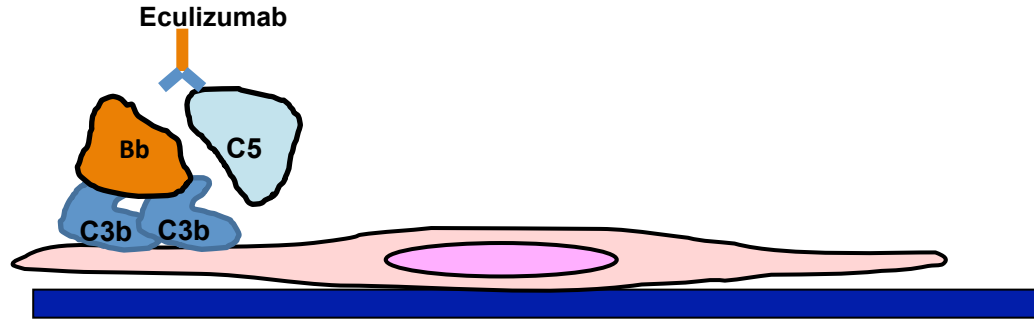**Does chronic « clinically-relevant » complement activation occur in all aHUS patients?**

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**Can eculizumab be discontinued in some patients
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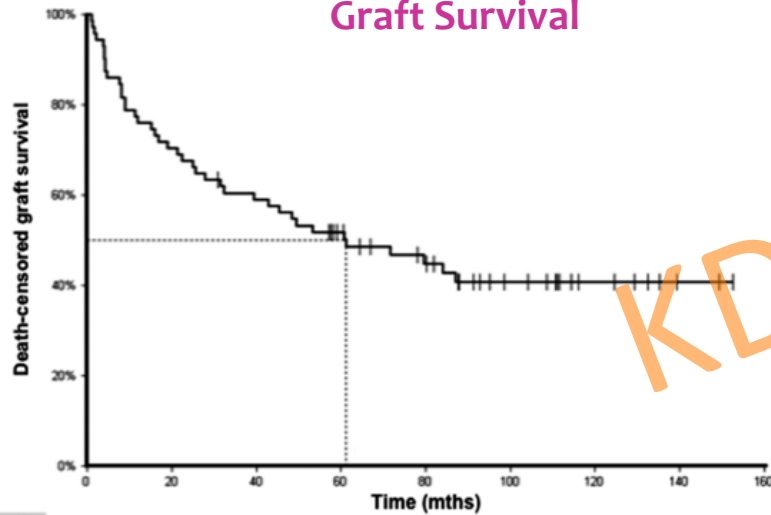**When a relapse has occured what is the optimal treatment strategy?**

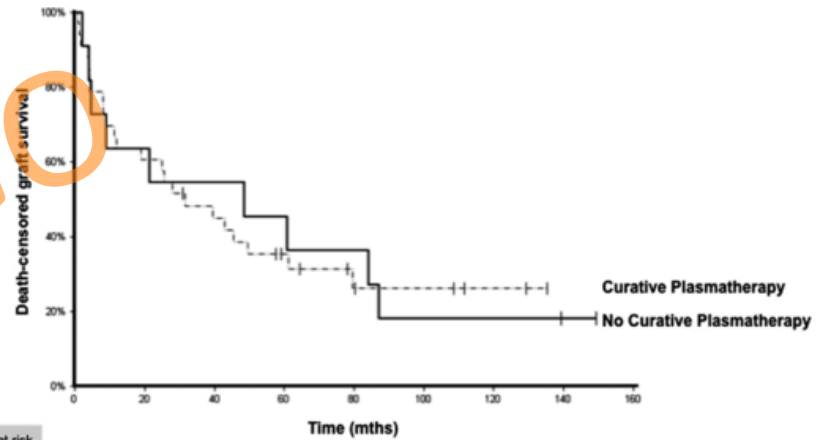# Issues in the treatment of aHUS

n = 57 aHUS pts + 71 RT

Renal transplantation in aHUS

Graft Survival
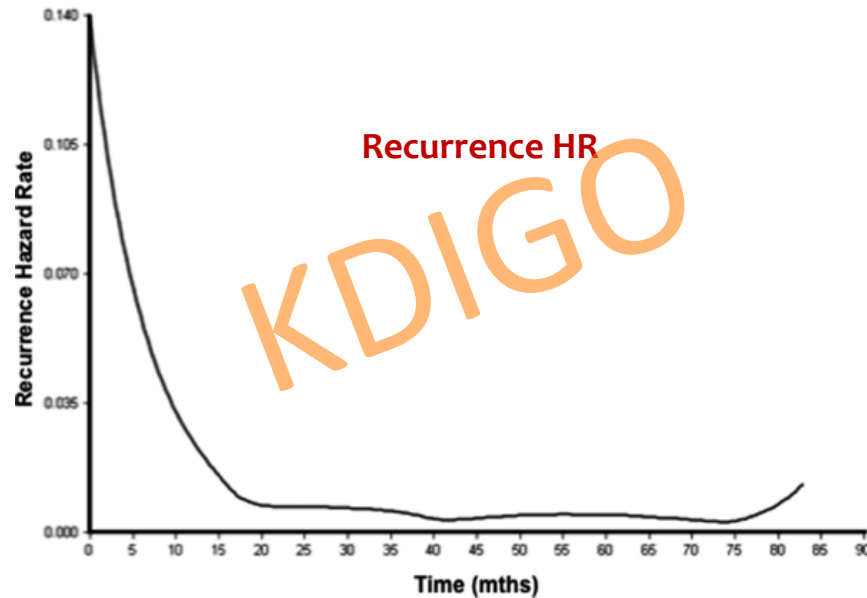
Le Quintrec M, AJT 2013

**Prophylactic use of eculizumab in high-risk patients for aHUS recurrence.
Combined liver-renal transplantation in selected patients?**

Issues in the treatment of aHUS

n = 57 aHUS pts + 71 RT

Renal transplantation in aHUS

Le Quintrec M, AJT 2013

Recurrence HR

Prophylactic use of eculizumab in high-risk patients for aHUS recurrence.
Combined liver-renal transplantation in selected patients?
Optimal duration of treatment in RT patients with aHUS?