Indications du plasma et du Ravulizumab dans le SHU atypique

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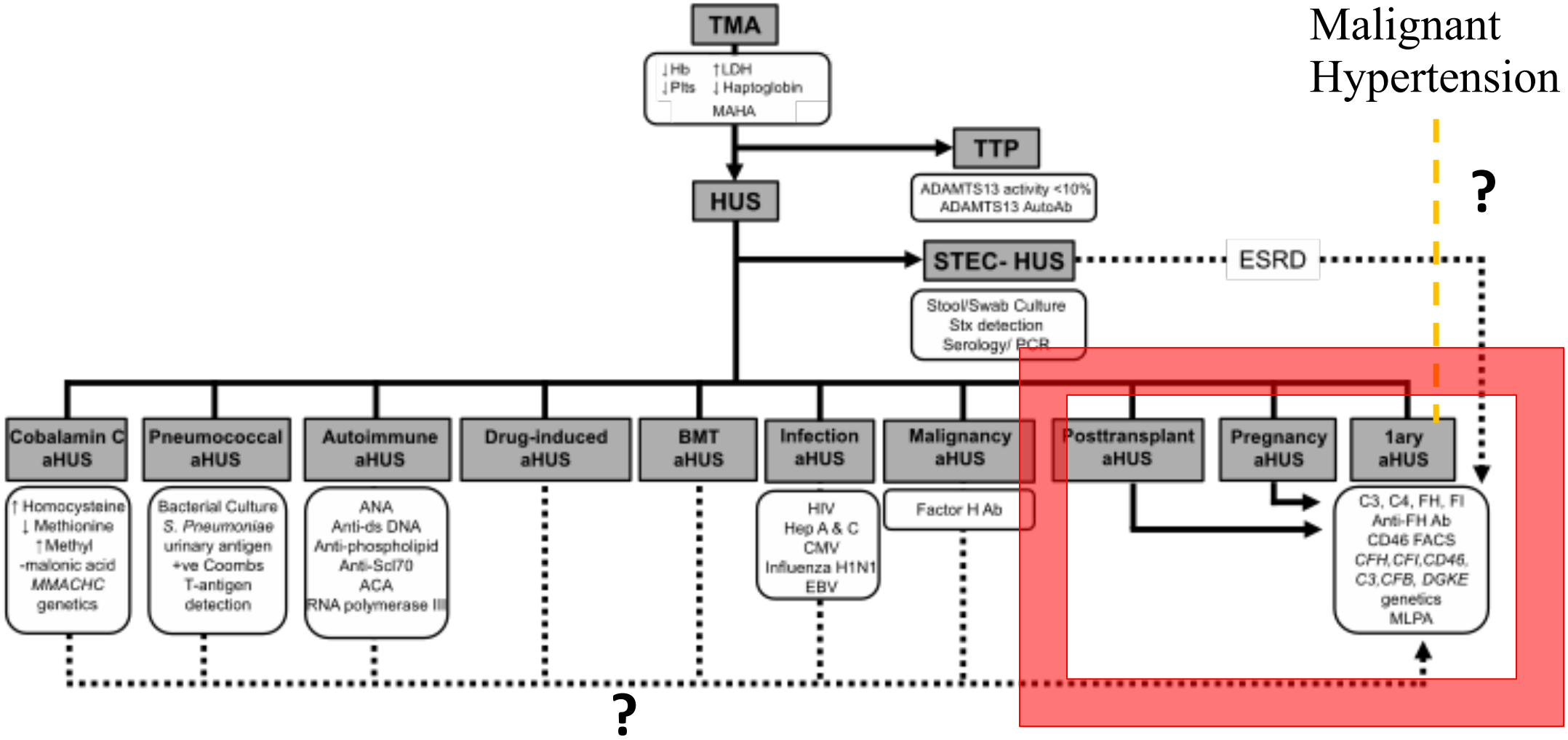
congrès de la Société Française d'Hémaphérèse l 10 novembre 2021

Conflicts of interest

- SANOFI:
  - Expertise
- Alexion : None

TMA diagnostic flow chart

KDIGO, Kidney Int, 2017



Predictive score of severe Adamsts13 deficiency

Patient characteristics	Adjusted OR	95% CI	p value
Creatinine <200 µmol/L (<2.26 mg/L)	23.4	8.8, 62.5	<0.001
Platelets <30 x 10^9/L	9.1	3.4, 24.8	<0.0001
Antinuclear antibodies +	2.8	1.0, 8.0	<0.01

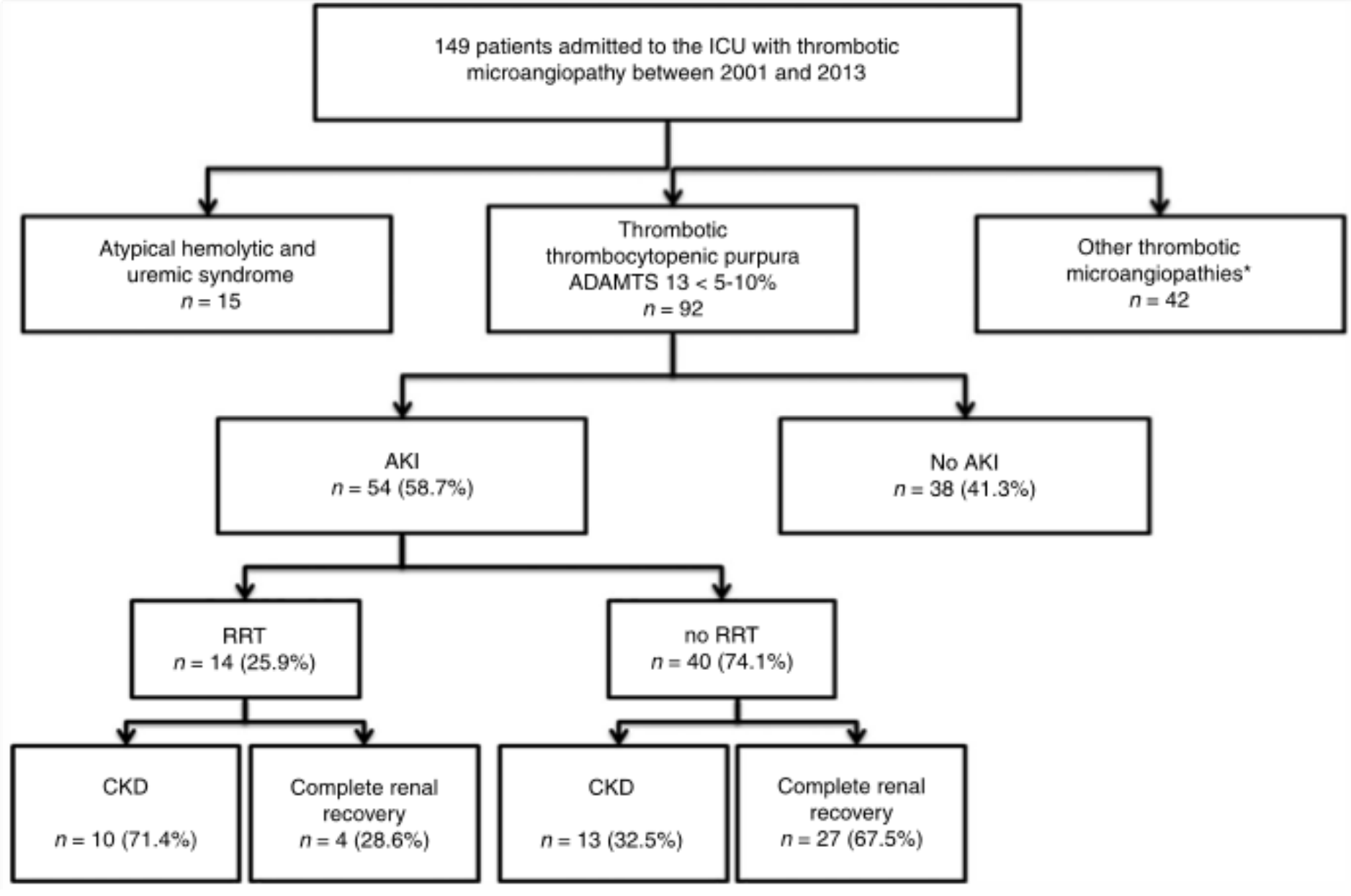
Sensitivity: 98.1%
Specificity: 48.1%

Positive predictive value: 85%
Negative predictive value: 93.3%

Early identification of patients with a severe, acquired ADAMTS13 deficiency

French TMA reference Center. *Medicine (Baltimore)* 2004;83:233-44
French TMA reference Center. *PLoS One* 2010;5:e10208

Flow chart of the 149 patients admitted to the ICU with thrombotic microangiopathy (TMA)
Zafrani, et al, J Thromb Haemost, 2014



Présentation clinique des SHU atypiques de la cohorte française

V. Frémeaux-Bacchi, CJASN, 2013

Table 1. Patients' characteristics at onset

Characteristic	Children	Adults	*P* Value
Patients (*n*)	89	125	
Female/male (*n*/*n*)	42/47	93/32	<0.001
Mean age at onset (yr)	1.5 (0 to <15)	31 (15–85)	
Familial HUS history, *n* (%)	24 (26.9)	18 (14.4)	0.02
Triggering events, *n* (%)	42 (47)	41 (33)	0.03
Diarrhea	35 (39)	19 (15)	<0.001
Respiratory infections	7 (8)	1 (1)	0.03
Pregnancy		18/93 females (19.3)	
Neurologic involvement, *n* (%)	14 (16)[a]	10 (8)	0.08
Mean serum creatinine (μmol/L)	257 (28–990) (*n*=82)	640 (111–2408) (*n*=113)	<0.001
Dialysis required, *n* (%)	48/81 (59)	93/115 (81)	<0.001
Platelets count, *n* (%)			
$> 150 \times 10^9$/L	12/81 (15)	15/93 (16)	0.78
$100–150 \times 10^9$/L	9/81 (11)	22/93 (24)	0.02
$50–99 \times 10^9$/L	26/81 (32)	31/93 (33)	0.84
$< 50 \times 10^9$/L	34/81 (42)	25/93 (27)	0.05
Mean hemoglobin (g/dl)	6.8 (3–12) (*n*=84)	7.2 (5–11.8) (*n*=93)	0.004
Hemoglobin > 10 g/dl, *n* (%)	5/84 (6)	10/93 (11)	0.16
Complete triad, *n* (%)[b]	60/81 (74)	77/93 (83)	0.11

Values are given as means with ranges in parentheses or as percentages. HUS, hemolytic uremic syndrome.

[a]In children, extrarenal manifestations also included pancreatitis (increase of pancreatic enzymes with or without clinical/radiologic signs) in six cases (7%), hepatitis (increase in hepatic enzymes) in five cases (6%), multiorgan failure in three cases (3%), intra-alveolar hemorrhage in two cases (2%), and pericarditis in one case (1%). Extrarenal manifestations other than neurologic are not documented in adults.

[b]Complete triad: hemoglobin < 10 g/dl plus platelet count < 150 G/L plus serum creatinine above the upper limit of normal.

Table 1 | Clinical characteristics at onset in children with Shiga toxin-producing *E. coli*-associated, anti-CFH autoantibody-associated, or atypical HUS

Clinical characteristics at onset	STEC-HUS[12]	Anti-CFH autoantibody-associated HUS[4,11,a]	aHUS with or without complement abnormalities[2,b]
Age	Mostly 6 months to 5 years	Mostly 5–13 years	MCP mutation: >1 year, mostly 2–12 years CFH and CFI mutation: mostly <2 years C3 mutation and no complement abnormality identified: any age DGKE mutation:[c] all <1 year
Diarrhea	95% Severe colitis: 10%	9.4%[11] to 53%[4] Abdominal pain and vomiting: 84%[4]	39%
Progressive onset	No	No	Possible
Complete triad[d]	~95%	100%	74%
Acute renal failure	95%, dialysis required in 50%	100%, dialysis required in 57%[4] to 86%[11]	85%, dialysis required in 60%
Neurological symptoms[e]	20%	23%[4] to 40.6%[11]	16%
Pancreatitis (elevated amylasemia/lipasemia)	10%	23%[4]	7%
Hepatitis (elevated transaminases ± jaundice)	10%	50%[4] to 57.3%[11]	6%
Cardiac involvement[f]	2–5%	Possible	2%
Familial HUS history	Simultaneous occurrence or a few days or weeks apart (familial contamination)	No	27% Complement mutations: autosomal dominant inheritance DGKE mutations: autosomal recessive inheritance

Loirat C, Frémeaux-Bacchi, V, Kidney Int, 2014

What are the etiologies and outcomes of thrombotic microangiopathies (TMA)?

CJASN
Clinical Journal of American Society of Nephrology

Methods and Cohort

Retrospective chart review 2009-2016

4 hospitals in France

564 patients with adjudicated TMA

6% Primary TMA
94% Secondary TMA

Results

Causes

Primary TMA

3% TTP

3% aHUS

Secondary TMA

35% Pregnancy

33% Infection

26% Drugs

19% Cancer

15% Transplant
9% Autoimmune

6% Shiga toxin
4% Malignant HTN

57% with multiple causes

Treatment

41% of all TMA
Red cell transfusion

94% of TTP
Plasma infusion or exchange

67% of aHUS
Eculizumab

Outcomes

15%
Dialysis

11%
Major CV Event

4%
Neurologic complications

10%
Death

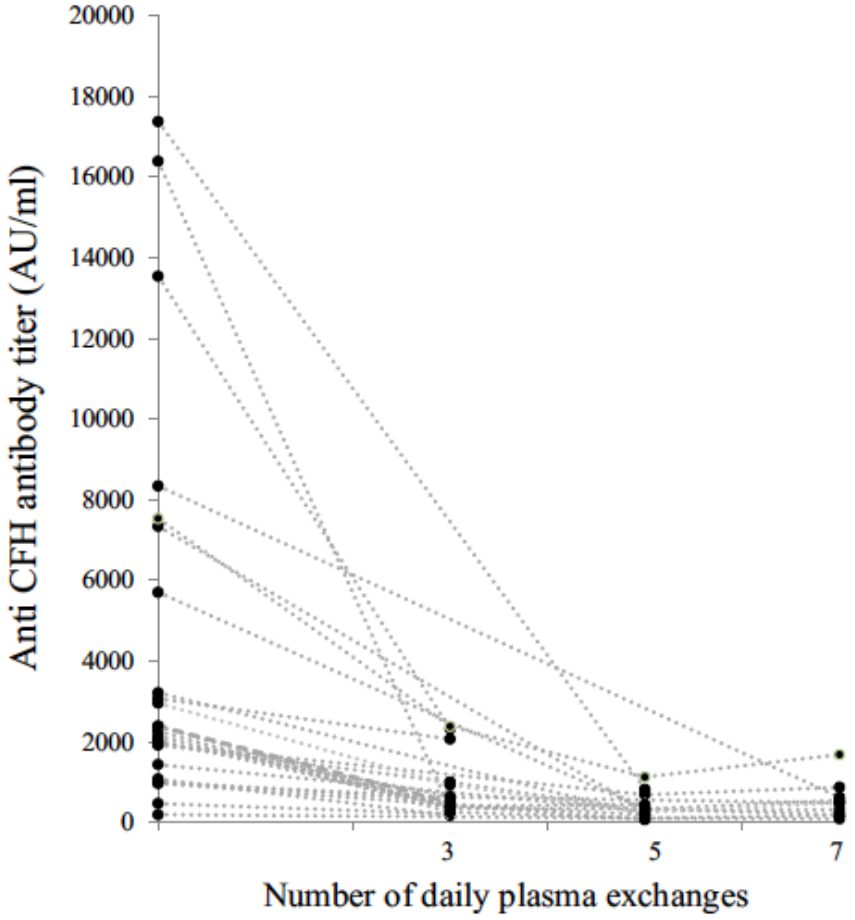
Complications varied widely by cause

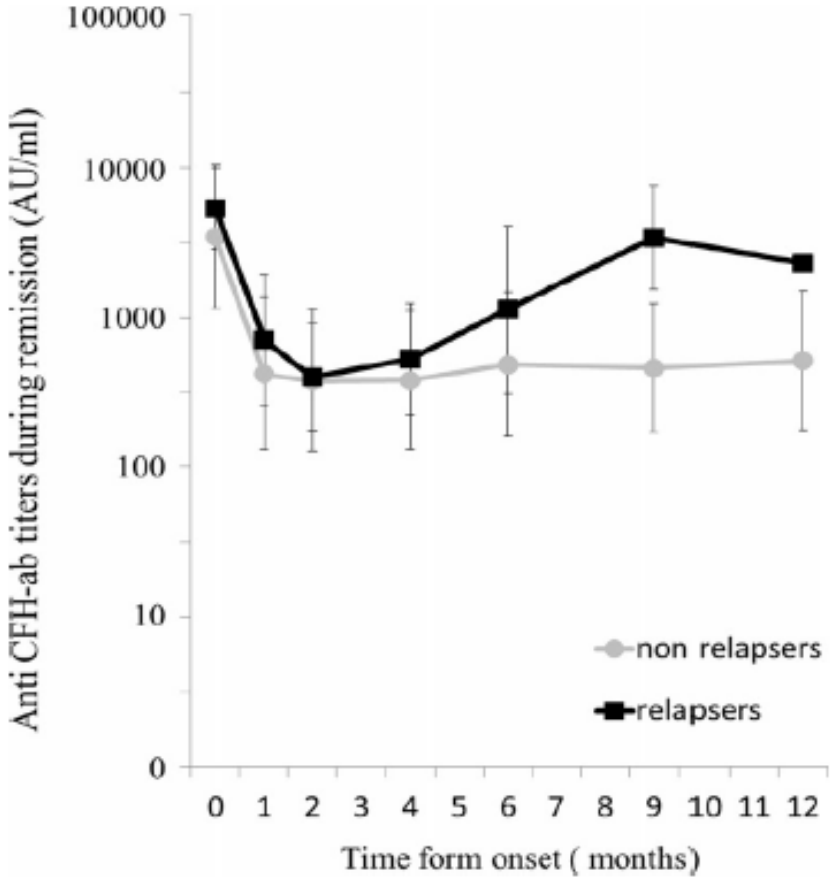
Conclusion Secondary TMA's represent the majority of TMA's. Multiple causes are present in half of secondary TMA's. The risk of dialysis, neurologic and cardiac complications, and death vary by cause.

Guillaume Bayer, Florent von Tokarski, Benjamin Thoreau, Adeline Bauvois, et al. ***Etiologies and Outcomes of Thrombotic Microangiopathies.*** CJASN doi: 10.2215/CJN.11470918. **Visual Abstract by Beatrice Concepcion, MD**

Anti-factor H antibody and aHUS (in children)

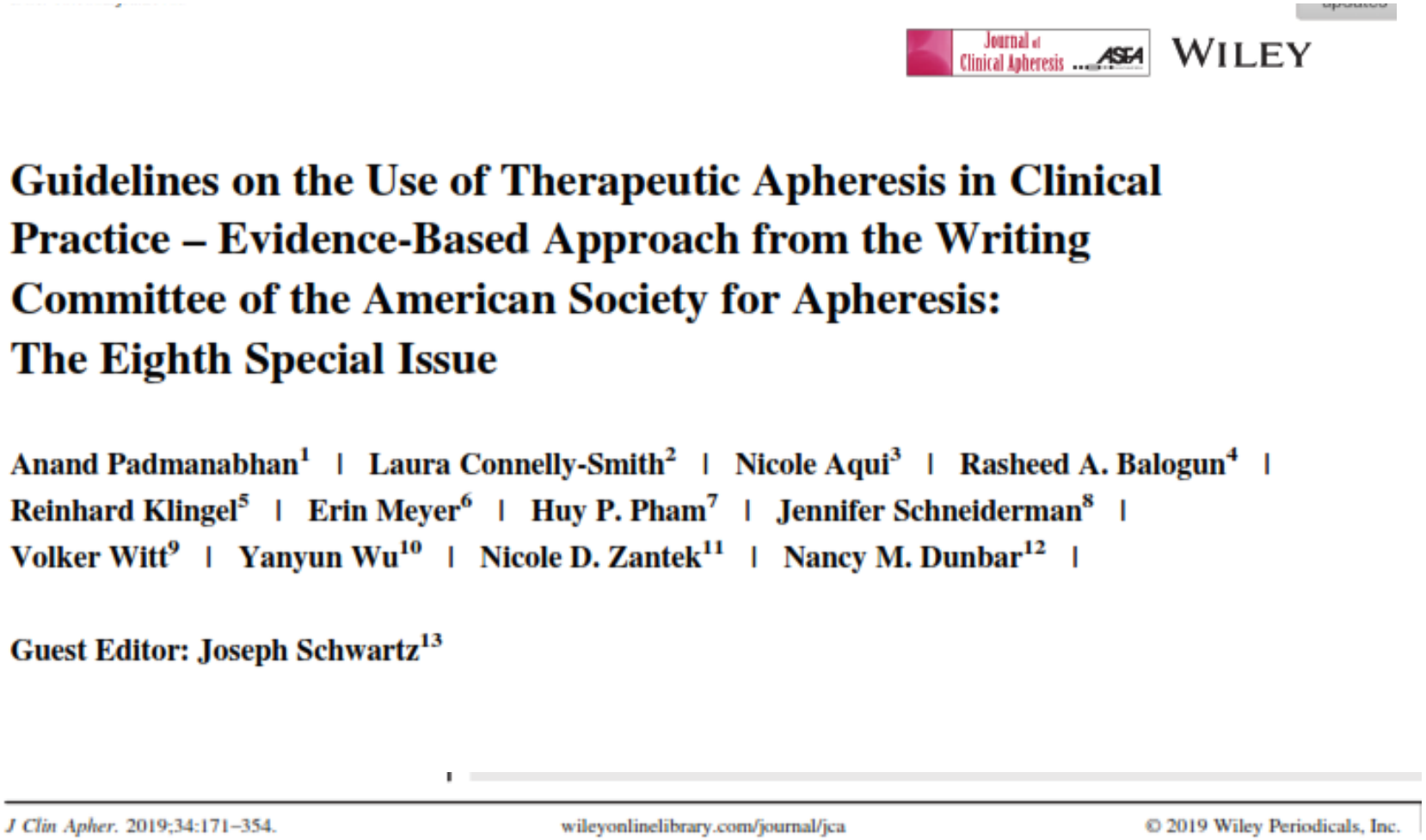
Therapy either with cyclophosphamide- (n=31) or rituximab-(n=14) based regimens were associated with similar outcomes and a comparable decline in antibody titers





Khandelwal P, Pediatr Nephrol (2015) 30:451–457

Echanges plasmatiques en Néphrologie



Journal of Clinical Apheresis — ASFA — WILEY

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue

Anand Padmanabhan[1] | Laura Connelly-Smith[2] | Nicole Aqui[3] | Rasheed A. Balogun[4] | Reinhard Klingel[5] | Erin Meyer[6] | Huy P. Pham[7] | Jennifer Schneiderman[8] | Volker Witt[9] | Yanyun Wu[10] | Nicole D. Zantek[11] | Nancy M. Dunbar[12] |

Guest Editor: Joseph Schwartz[13]

J Clin Apher. 2019;34:171–354. wileyonlinelibrary.com/journal/jca

Indications néphrologiques pour les EP

TABLE 2 Category Definitions for Therapeutic Apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

IRB = Institutional Review Board

1- Catégories des Indications des aphérèses thérapeutiques – Guidelines ASFA 2019

2-Niveau de preuve associé

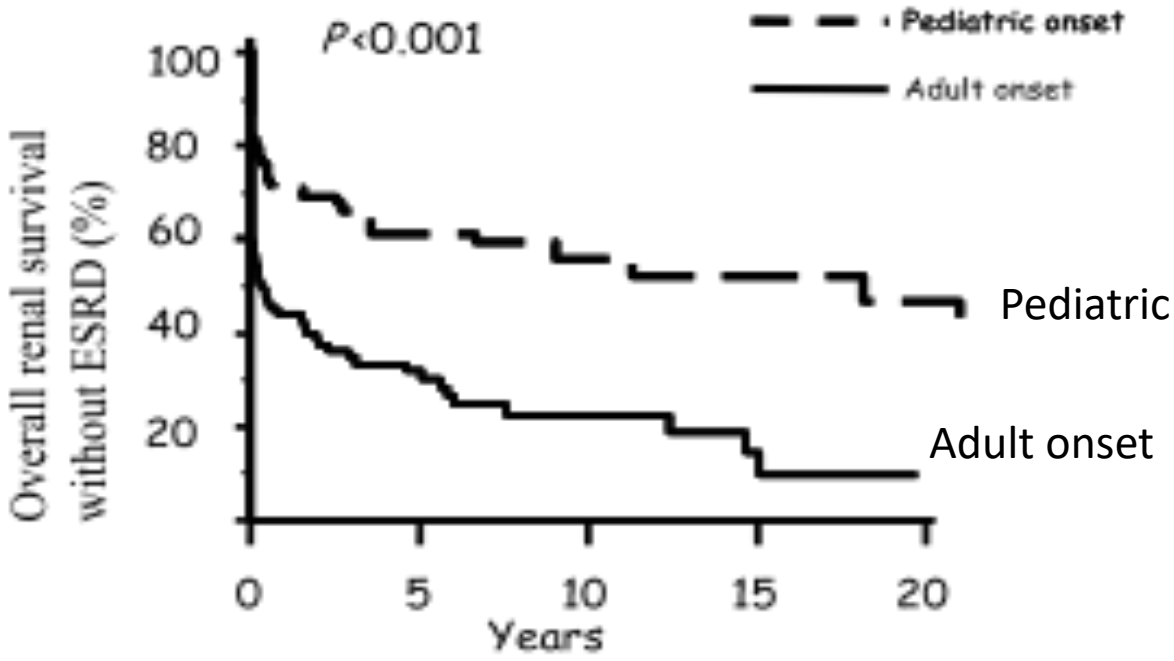
Niveau 1 recommandation forte **Niveau 2** recommandation faible
A : Niveau de preuve élevé (Etudes randomisées)
B: Niveau de preuve modéré (Etudes cas-contrôle)
C: Niveau de preuve faible (Cas clinique)

Niveau de recommandations selon Guyatt et al.

	1A	1B	1C	2A	2B	2C
I	Vascularite ANCA (créat>500µmol/l) **PTT**	Rejet aigu hum Sd hyperviscosité Goodpasture HSF greffon Désensibilisation HLA (DV) Greffe ABO i (DV)	Périartérite noueuse	Cryoglobuline		**SHU atypique (ac anti CFH) (enfants+++)**
II					Tubulopathie myélomateuse	Lupus sévère Syndrome catastrophique antiphospholipides
III					GN CIC GN IgA	**SHU post-infectieux** Sclérodermie Fibrose systémique néphrogénique Purpura rhumatoide Désensibilisation HLA (DD) **SHU atypique (variant génétique)**
IV		Greffe ABO incompatible (DD)				

Cumulative Kaplan-Meier estimates of the rates of patients without ESRD or death according to the age at onset

despite plasmatherapy



Number of aHUS patients at risk

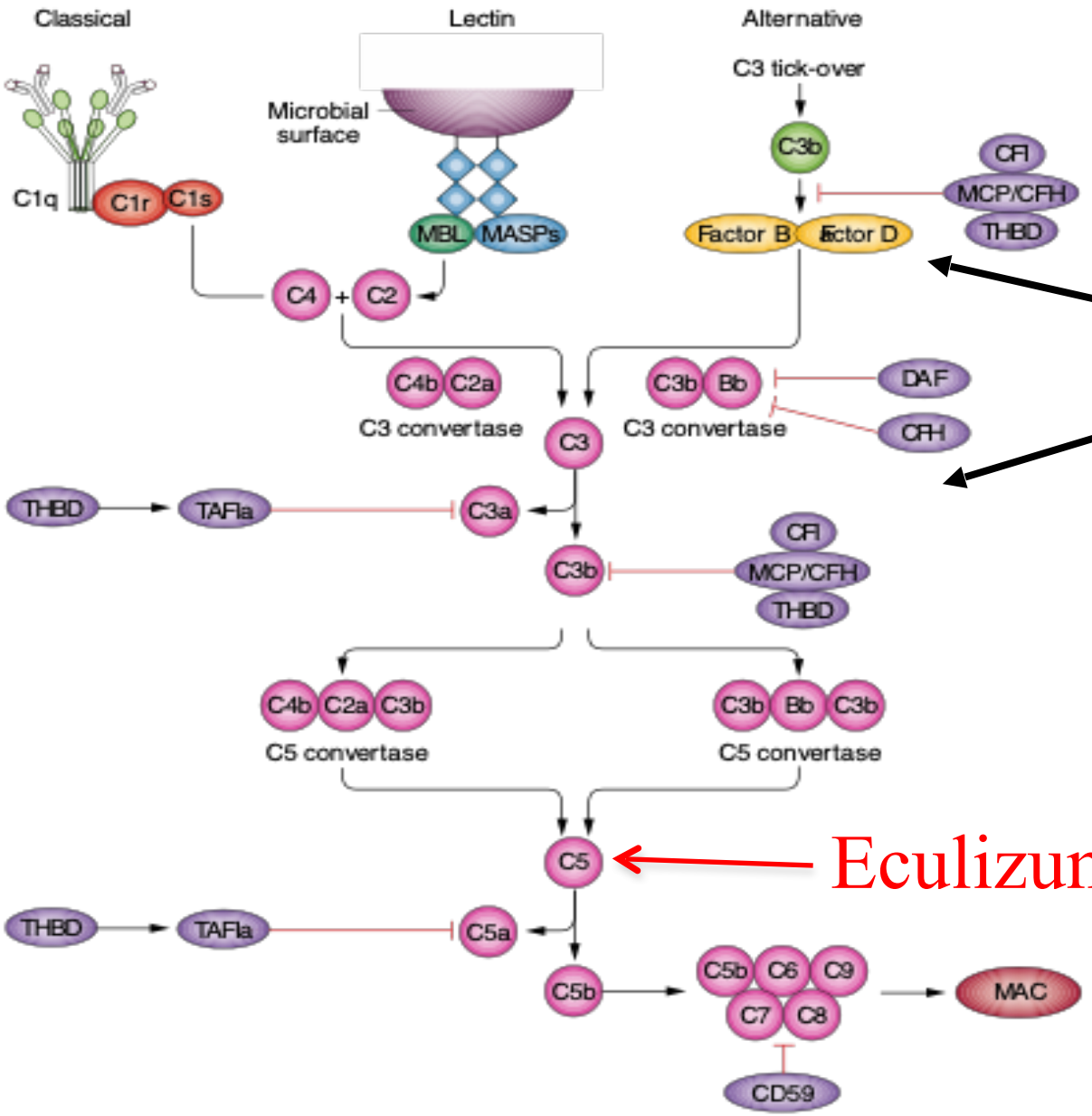
Pediatric onset	89	34	17	13	6
Adult onset	125	18	7	2	0

V. Frémeaux-Bacchi, CJASN, 2013

Therapeutic approachs in aHUS

- Symptomatic treatments:
  - Blood pressure control
  - Renal replacement therapy
- Etiopathogenic treatments:
  - Plasma exchanges:
    - At the early phase of TMA (adults)
    - During diagnostic work up (before ADAMTS-13 results, and elimination of STEC-induced HUS, anti-CFH mediated aHUS, and secondary HUS)
  - Complement blockers
    - Anti C5 drugs
    - Future treatments: Other targeted treatments such as Anti CFB or anti CFD drugs ?

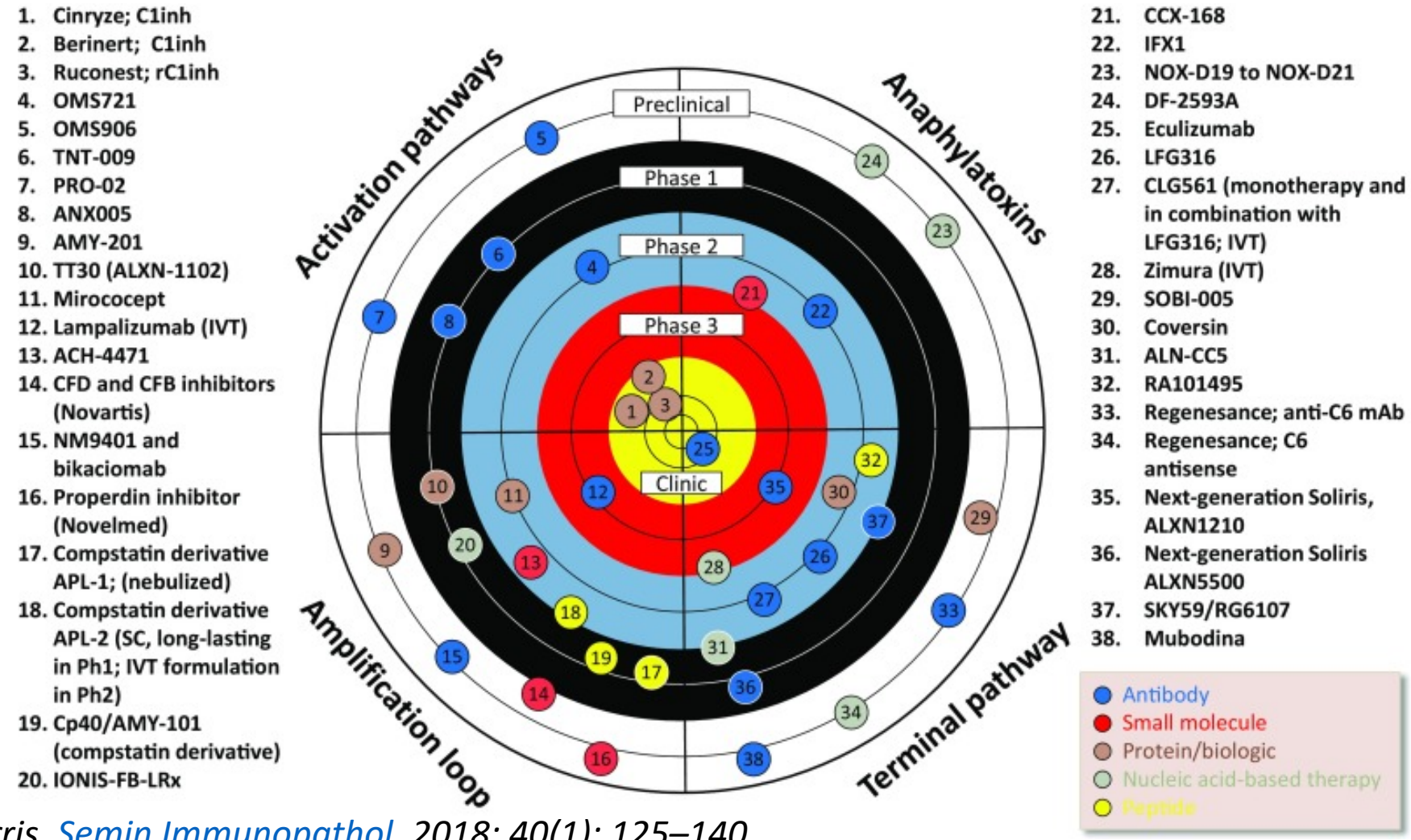
The complement cascade: 3 pathways



Proximal inhibitors

Eculizumab, ravulizumab

The current complement drug development landscape



Claire C Harris, Semin Immunopathol. 2018; 40(1): 125–140

List of molecules targeting C5, C5a or C5aR1 tested in prospective trials

- Monoclonal (humanized) antibodies:
  - Eculizumab
  - Ravulizumab
  - Crovalimab
  - Pozelimab, Tesidolumab
  - Biosimilars of eculizumab
- Proteins and peptides:
  - Nomacopan
  - Zilucoplan
- Oligonucleotides:
  - Cemdisiran
  - Avacincaptad pegol

- IFX-1: C5a-targeting antibody
- Avacopan, C5aR1-targeting small molecule
- Avdoralimab, C5aR1-targeting antibody
- HMR59 (AAVCAGsCD59), MAC-targeting gene therapy

Ort, et al, Frontiers in Immunology, December 2020 | Volume 11 | Article 599417

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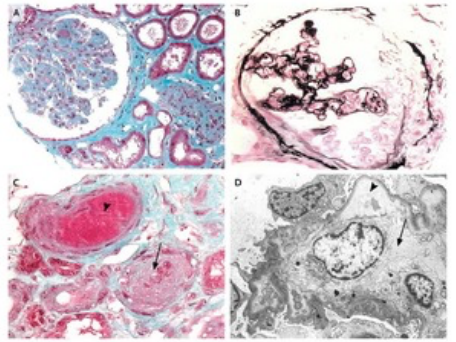
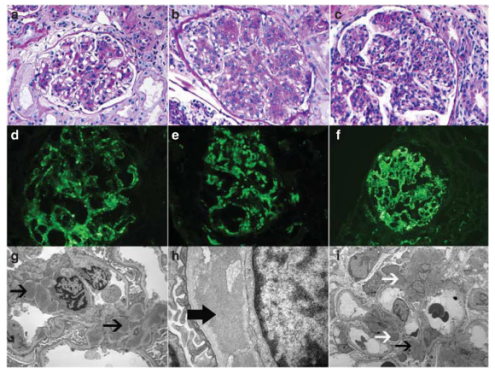
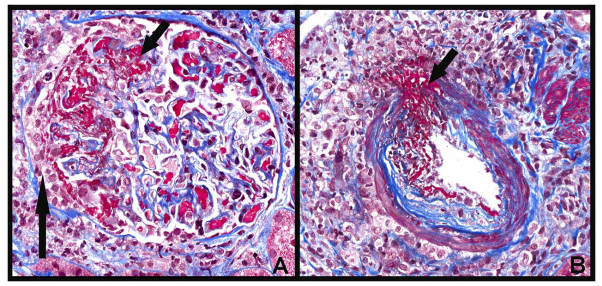
Ort, et al, Frontiers in Immunology, December 2020 | Volume 11 | Article 599417

Main renal diseases evaluated in clinical trials targeting complement

- Atypical HUS
- C3 glomerulonephritis
- ANCA-associated vasculitis
- IgA nephritis
- IC-MPGN
- Lupus nephritis
- Membranous nephropathy
- Ischemic reperfusion injury
- Antibody mediated rejection



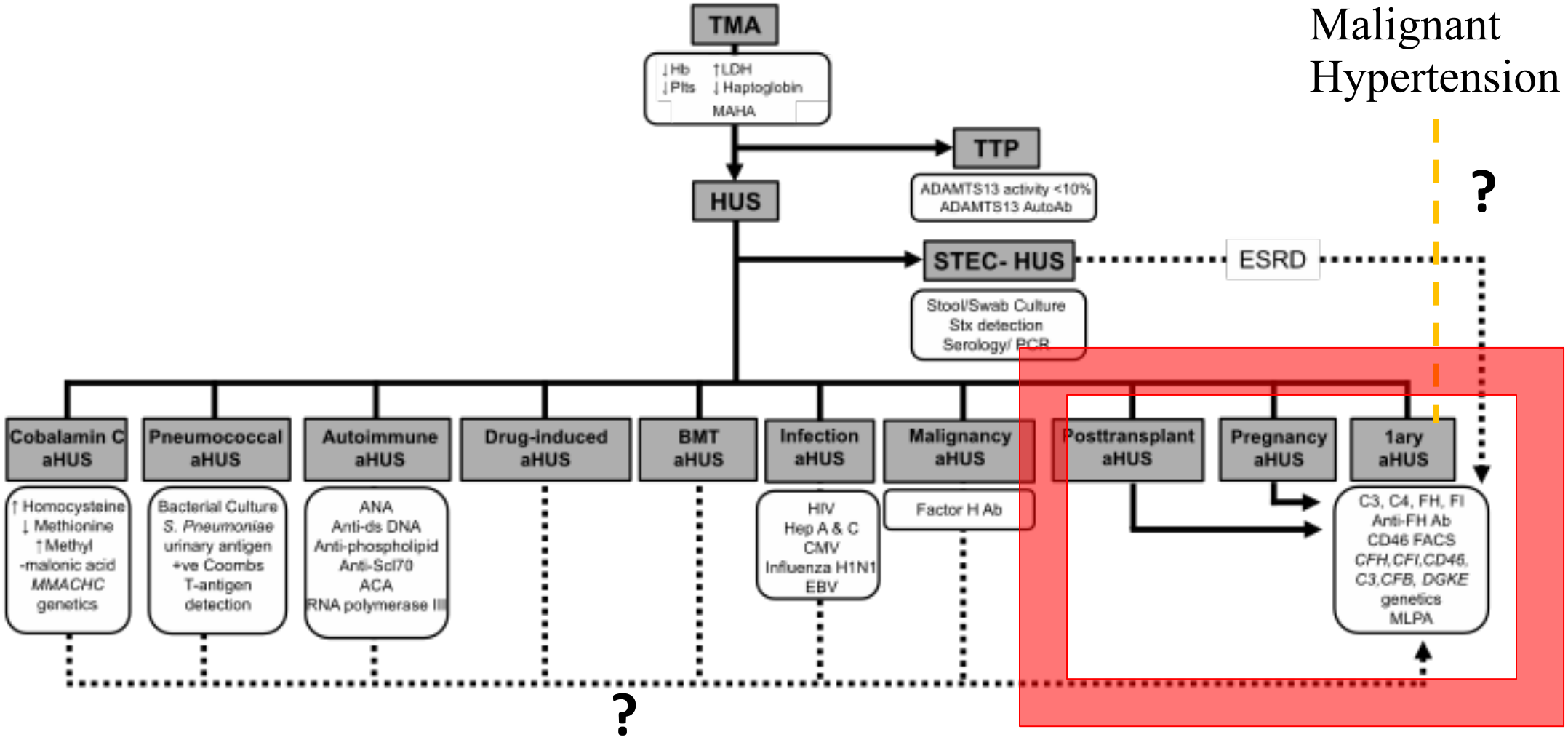




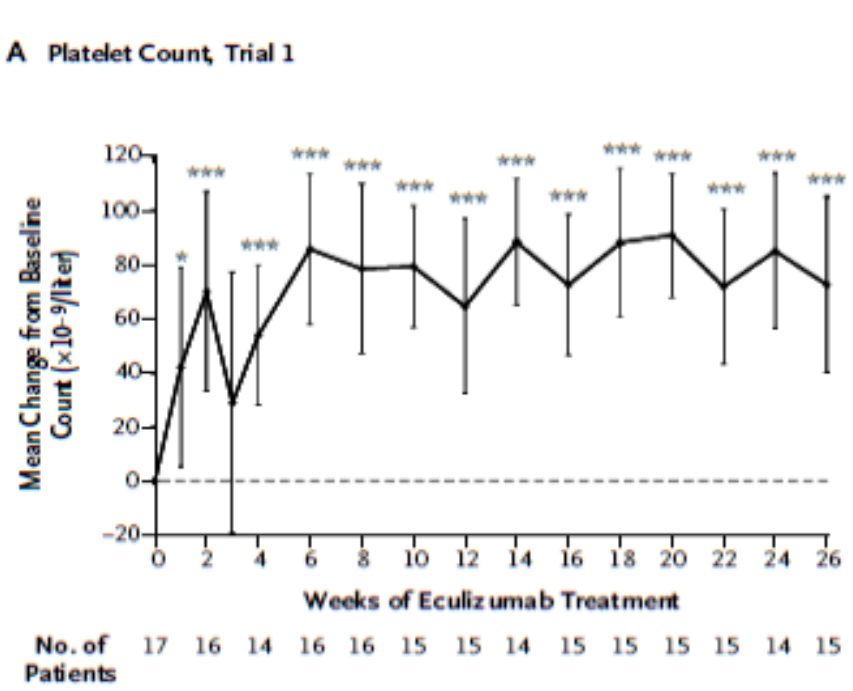
Zipfel, PF, Frontiers in Immunology, 2019

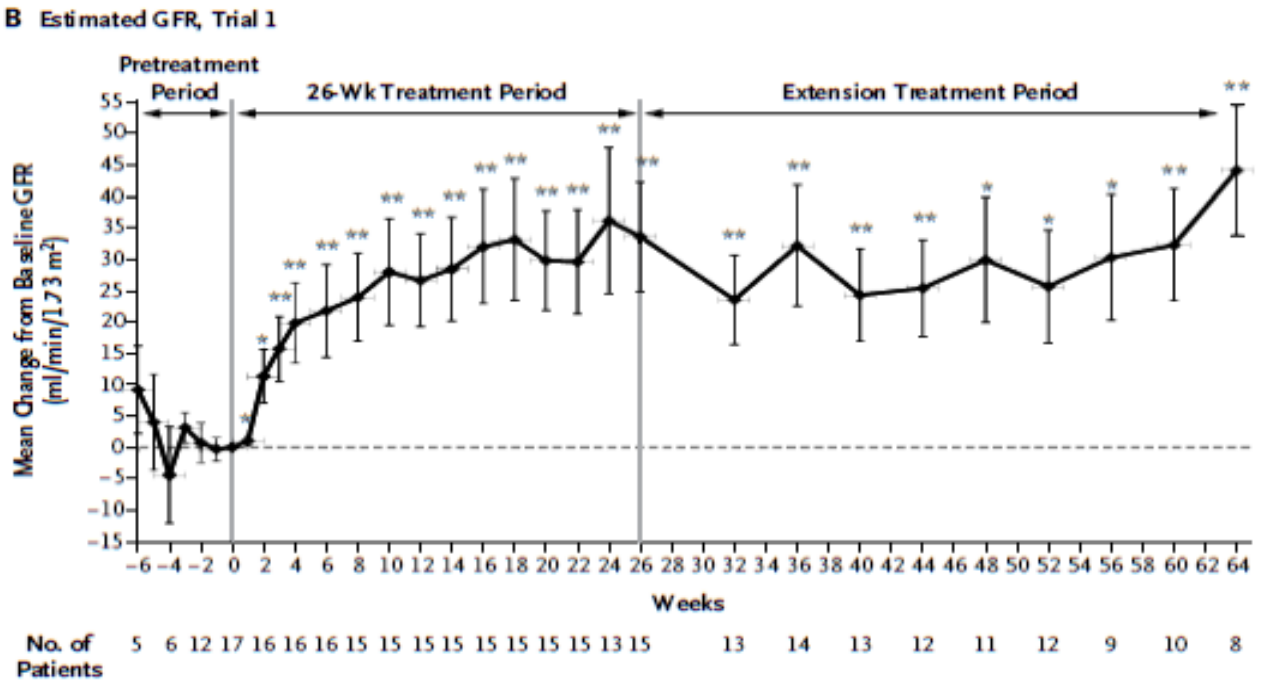
TMA diagnostic flow chart

KDIGO, Kidney Int, 2017



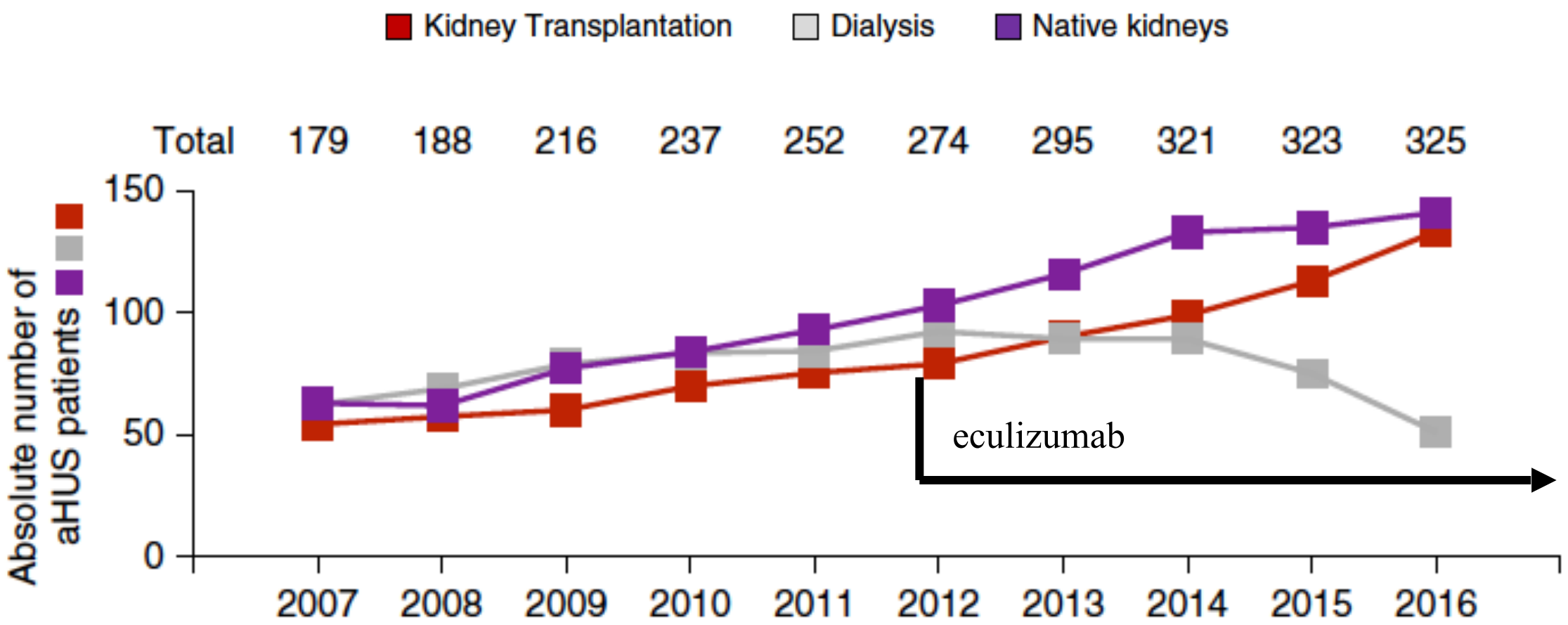
Eculizumab in aHUS





Legendre C, NEJM, 2013

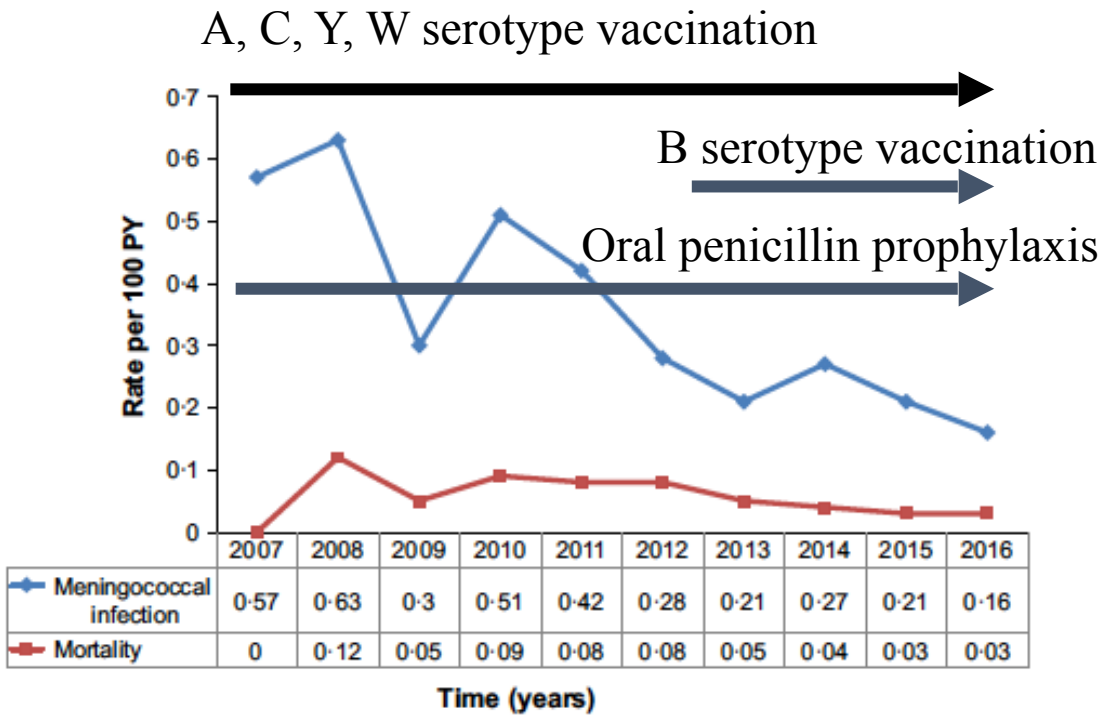
A dramatic change in the renal status of aHUS patients between 2007 and 2016



Zuber, J, JASN, 2019

Drawbacks of eculizumab treatment

Meningoccocal infections: N= 76 cases including 8 fatal cases



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Meningococcal infection	0·57	0·63	0·3	0·51	0·42	0·28	0·21	0·27	0·21	0·16
Mortality	0	0·12	0·05	0·09	0·08	0·08	0·05	0·04	0·03	0·03

Treatment burden:

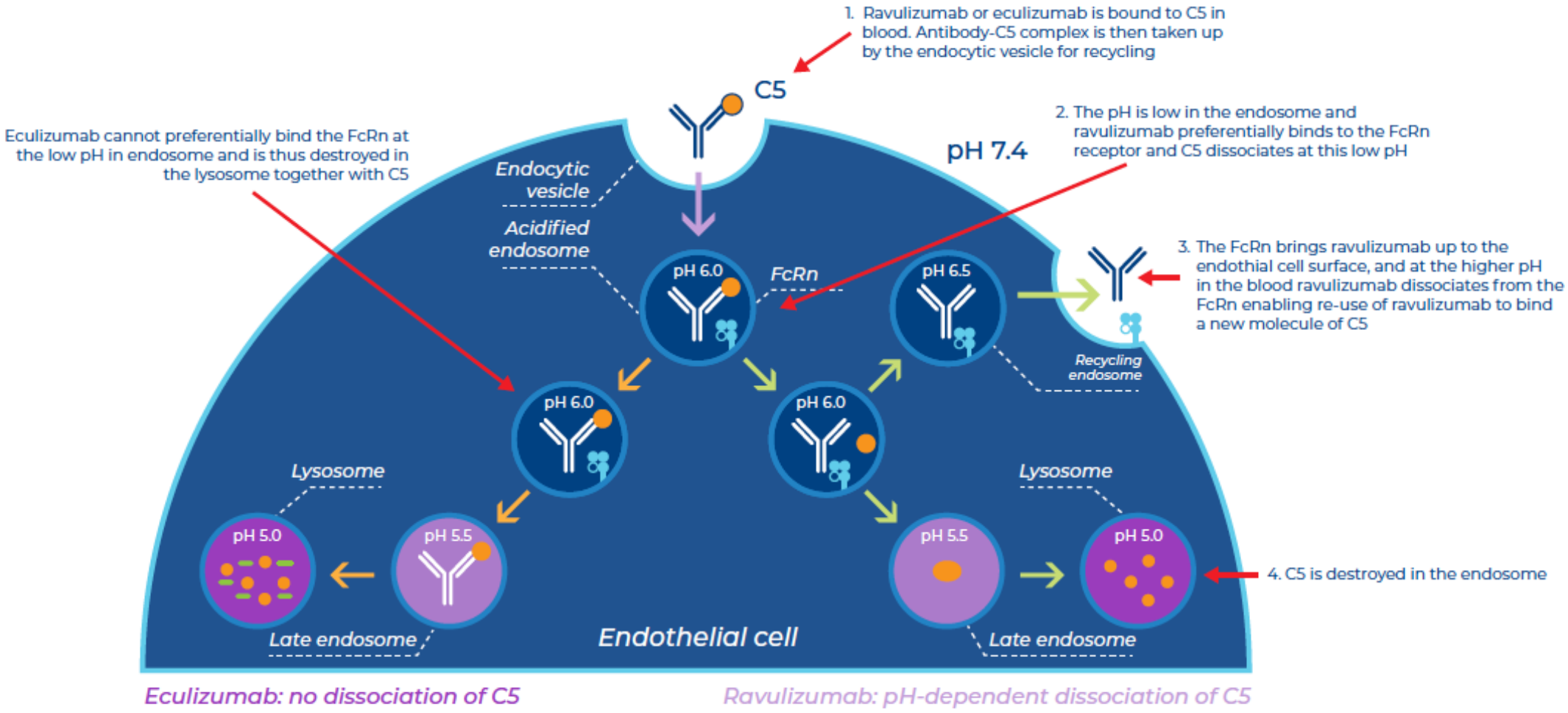
- Every 2 week injections
- Vascular access

Socie, G, Br J Hematol, 2019

A « new » C5 inhibitor (Alexion): ravulizumab

- engineered from eculizumab (humanized monoclonal antibody)
- targeting the same epitope (C5) as eculizumab with an extended half-life
  - 2 amino acid substitutions made to preserve high binding affinity to C5 in serum at pH 7.4 and permit dissociation of C5 from ravulizumab in the acidified endosome at pH 6.0
  - 2 further amino acid substitutions made to enhance affinity for neonatal Fc receptor (FcRn) at pH 6.0 and increase antibody recycling
- One IV injection every 8 weeks, compared to every 2 weeks with eculizumab

Ravulizumab has an increased duration of action and half-life compared to eculizumab based on a pH-dependent recycling of the antibody



C5, complement protein 5; FcRn, Fc receptor.

Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the #301 study

Jong Wook Lee,[1] Flore Sicre de Fontbrune,[2] Lily Wong Lee Lee,[3] Viviani Pessoa,[4] Sandra Gualandro,[5] Wolfgang Fürede[r,6] Vadim Ptushkin,[7] Scott T. Rottinghaus,[8] Lori Volles,[8] Lori Shafner,[8] Rasha Aguzzi,[8] Rajendra Pradhan,[8] Hubert Schrezenmeier,[9,10] and Anita Hill[11]

#NCT02946463. (Blood. 2019;133(6):530-539)

- Phase 3, open-label study assessing the noninferiority of ravulizumab vs eculizumab.
- In complement inhibitor–naive adults with paroxysmal nocturnal hemoglobinuria (PNH).

Results:

1- Ravulizumab was non- inferior to eculizumab for both coprimary and all key secondary end points

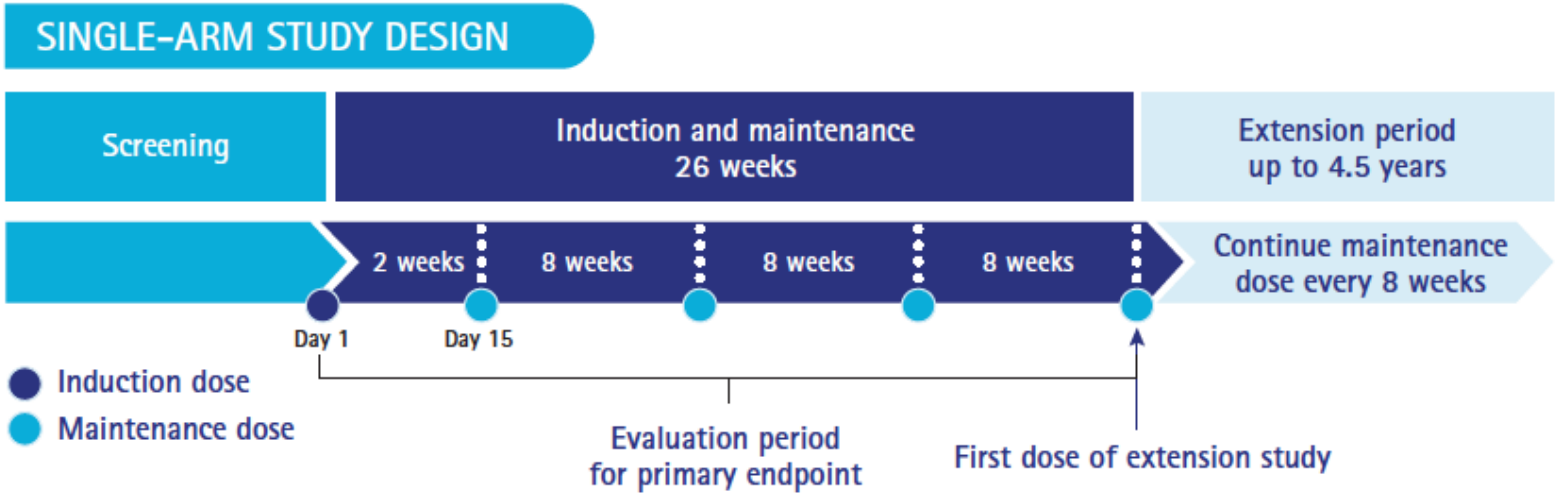
2- The safety and tolerability of ravulizumab and eculizumab were similar

The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment

#311 study

Eric Rondeau[1], Marie Scully[2], Gema Ariceta[3], Tom Barbour[4], Spero Cataland[5], Nils Heyne[6], Yoshitaka Miyakawa[7], Stephan Ortiz[8], Eugene Swenson[9], Marc Vallee[10], Sung-Soo Yoon[11], David Kavanagh[12] and Hermann Haller[13]; on behalf of the 311 Study Group[14]

Kidney Int, 2020



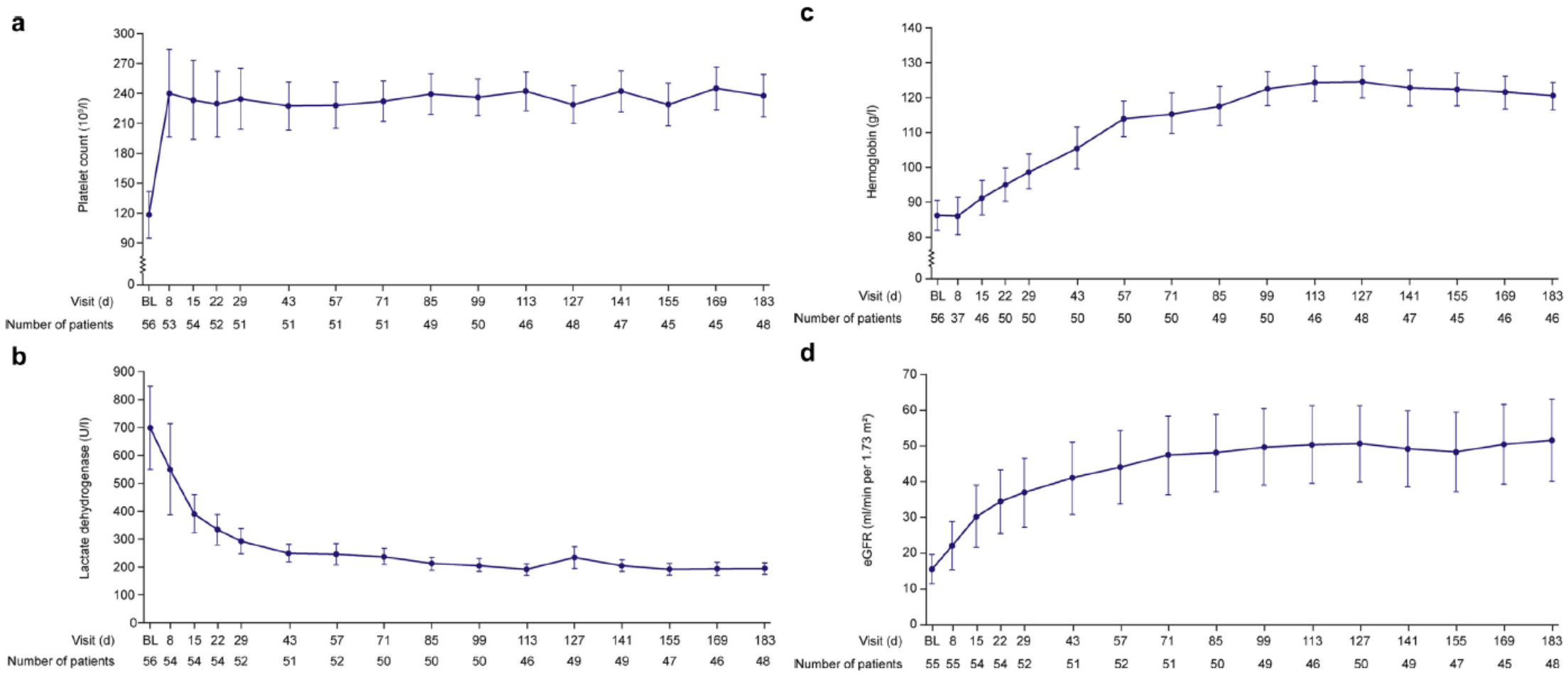
Patient body weight (kg)	Induction phase (mg)	Maintenance phase (mg)
≥40 to <60	2400	3000
≥60 to <100	2700	3300
≥100	3000	3600

ALXN1210-aHUS-311 (NCT02949128; EudraCT 2016-002027-29)

- Phase III, single-arm, global study evaluating the efficacy and safety of ravulizumab administered by i.v. infusion to adults

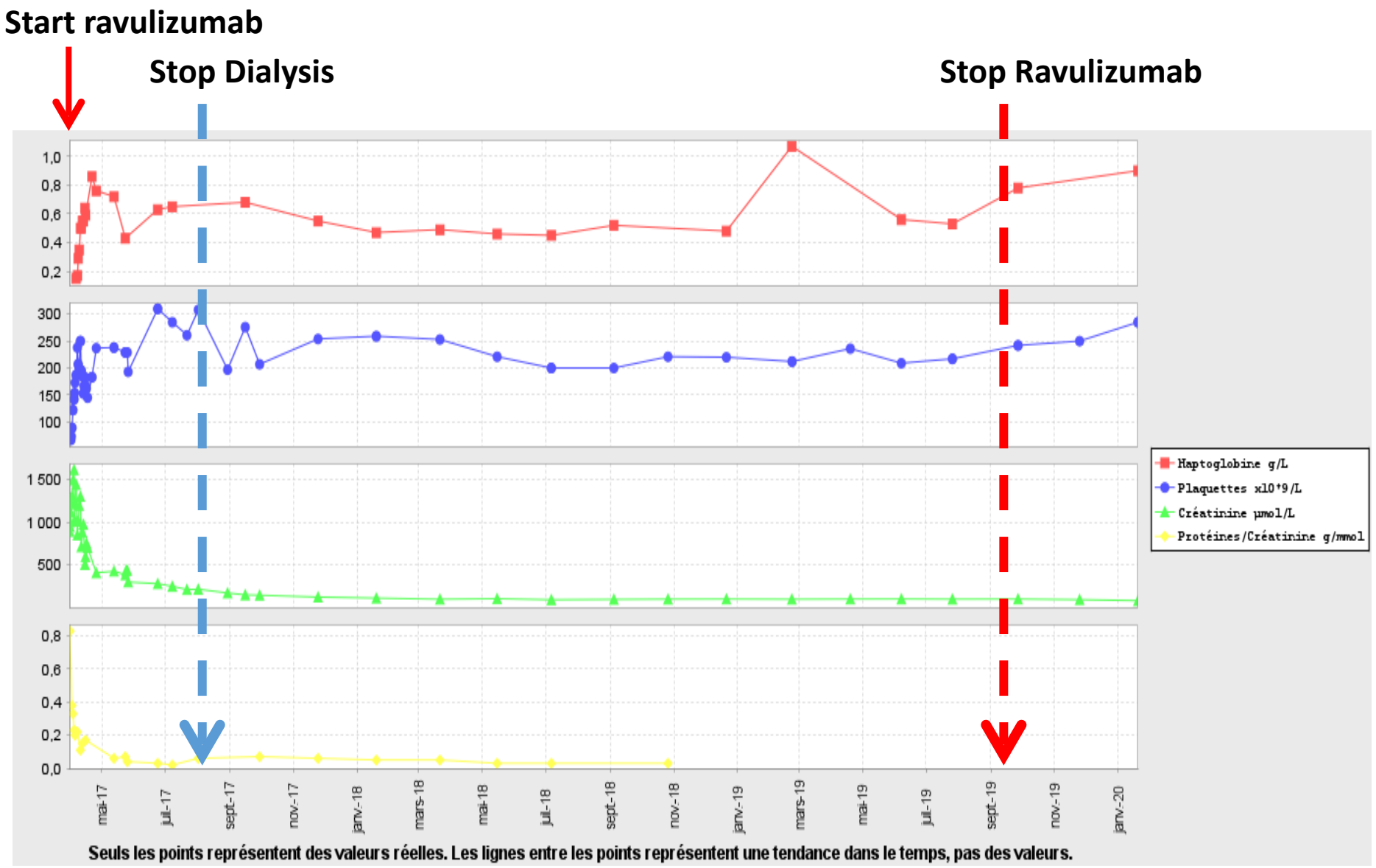
- with aHUS who are naive to complement inhibitor treatment.

Evolution of biological parameters with time



Rondeau, E, Kidney Int, 2020

Mrs N….(familial form, pathological MCP variant)



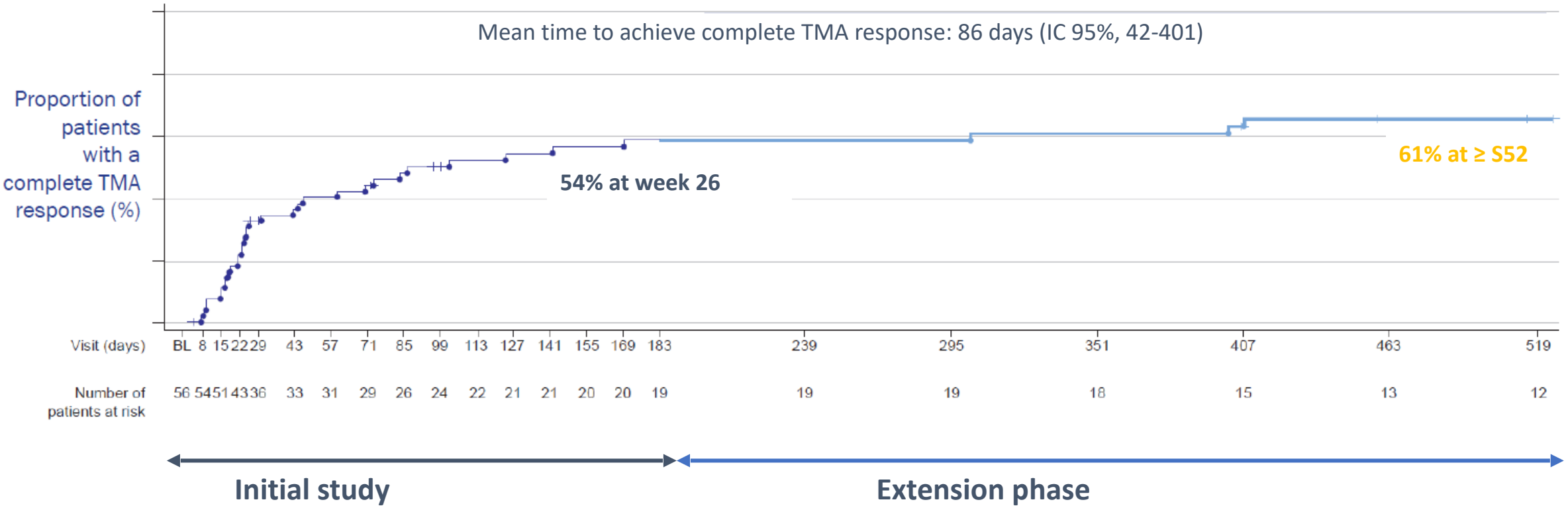
Tenon hospital

Improvement in eGFR category compared to baseline was seen in 32 of 47 (68.1%) patients with available data; 17 of 29 patients (58.6%) on dialysis at baseline came off dialysis by day 183

eGFR categories at baseline (N=47)		eGFR categories at Day 183					
		1 (≥90)	2 (60–89)	3a (45–59)	3b (30–44)	4 (15–29)	5 (<15)
1 (≥90)	0 (0.0)						
2 (60–89)	3 (6.4)	2 (4.3)	1 (2.1)				
3a (45–59)	1 (2.1)	1 (2.1)					
3b (30–44)	2 (4.3)	2 (4.3)					
4 (15–29)	7 (14.9)	1 (2.1)			3 (6.4)	1 (2.1)	2 (4.3)
5 (<15)	34 (72.3)	6 (12.8)	6 (12.8)	3 (6.4)	3 (6.4)	5 (10.6)	11 (23.4)

Rondeau, E, Kidney Int, 2020

#311 study: Long term results (> 52 weeks)



Barbour, T, Kidney Int Rep, 2021

Adverse events (#311 study)

Table 3 | Summary of adverse events reported

Category	Overall (N = 58) n (%)	Events
Any AE	58 (100.0)	818
Treatment-related	20 (34.5)	58
Not treatment-related	58 (100.0)	760
Any SAE	30 (51.7)	71
Fatal TEAE	3 (5.2)	3
Fatal pretreatment SAE	1 (1.7)	1
Meningococcal infection	0 (0.0)	0
AE severity		
Grade 1	54 (93.1)	454
Grade 2	46 (79.3)	223
Grade 3	31 (53.4)	116
Grade 4	14 (24.1)	22
Grade 5	3 (5.2)	3

Table 4 | Most frequent treatment-emergent adverse events

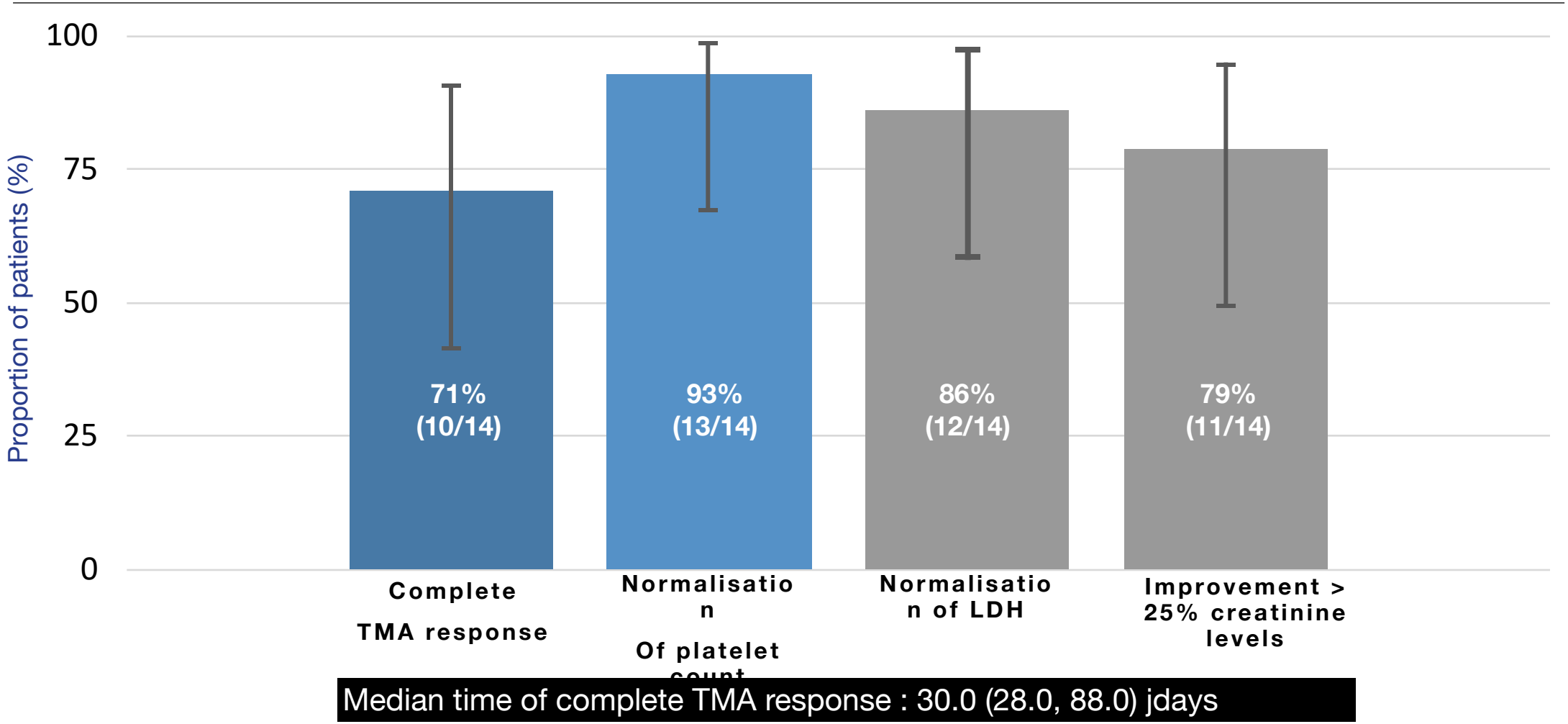
Adverse event term	Overall (N = 58) n (%)	Events
Headache	21 (36.2)	28
Diarrhea	18 (31.0)	24
Vomiting	15 (25.9)	18
Hypertension	13 (22.4)	20
Nausea	13 (22.4)	16
Urinary tract infection	10 (17.2)	21
Dyspnea	10 (17.2)	13
Arthralgia	10 (17.2)	12
Pyrexia	10 (17.2)	11
Cough	10 (17.2)	10
Hypokalemia	9 (15.5)	18
Edema peripheral	9 (15.5)	13

Table 5 | Most frequent treatment-emergent serious adverse events

Adverse event term	Overall (N = 58) n (%)	Events
Hypertension	3 (5.2)	5
Pneumonia	3 (5.2)	3
Malignant hypertension	2 (3.4)	5
Urinary tract infection	2 (3.4)	4
Septic shock	2 (3.4)	2
aHUS	2 (3.4)	2

Rondeau, E, Kidney Int, 2020

Effect of ravulizumab in children/adolescents (#312 study)



Ariceta, G, Kidney Int, 2020

Efficacy and safety of the long-acting C5 inhibitor ravulizumab in patients with atypical hemolytic uremic syndrome triggered by pregnancy: a subgroup analysis

Anja Gäckler[1*], Ulf Schönermarck[2], Vladimir Dobronravov[3], Gaetano La Manna[4], Andrew Denker[5], Peng Liu[5], Maria Vinogradova[6], Sung-Soo Yoon[7] and Manuel Praga[8]

8 pregnancies p-aHUS

Median age of 37.7, postpartum aHUS
Receiving Ravulizumab soon after delivery (median 11 [range, 5–19] days),

1 CFB
1 FHab
6 undeterminated

Stratégie de traitement par Anti-C5 dans le SHUa

- Combien de temps faut il traiter ?
  - Au moins 6 mois

- Peut on arrêter les anti-C5 ? OUI, sous surveillance
  - Bandelette urinaire 2 fois/semaine
  - Biologie: tous les 8 jours X 1 mois, puis tous les 15 jours X 2 mois, puis tous les mois X 1 an

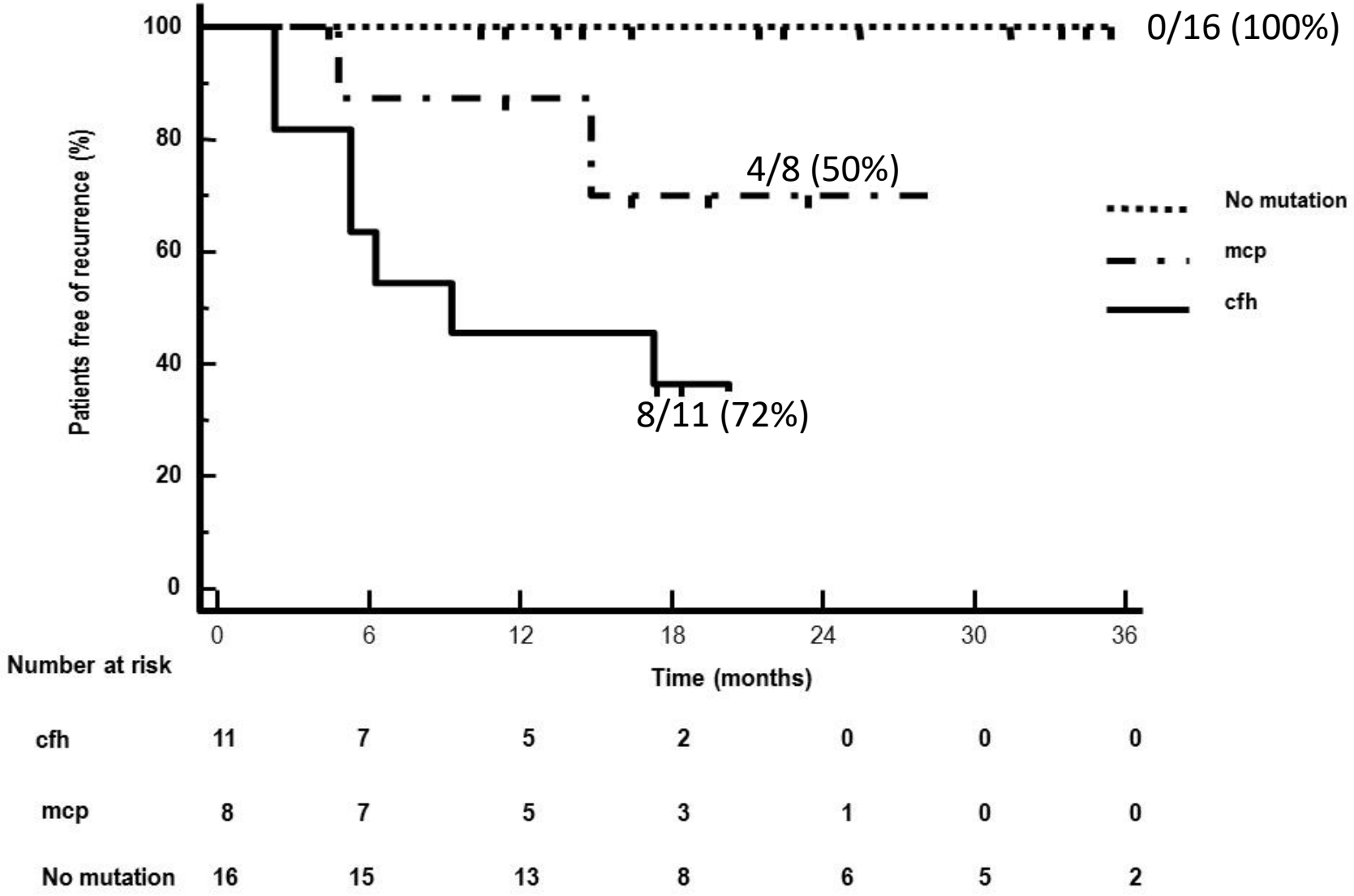
aHUS relapse-free survival after eculizumab discontinuation in patients with *cfh*, *mcp* or no detected mutations (n=38)

(Fakhouri et al, CJASN, 2017)

Duration of Ecu treatment:
17.5 months (2-50)

Mediane time to relapse:
6.6 months (3-22)

Relapsers in adults are younger and
had previous history of relapse



> Blood. 2020 Dec 3;blood.2020009280. doi: 10.1182/blood.2020009280. Online ahead of print.

Eculizumab discontinuation in children and adults with atypical haemolytic uremic syndrome: a prospective multicentric study

Fadi Fakhouri [1], Marc Fila [2], Aurelie Hummel [3], David Ribes [4], Anne-Laure Sellier-Leclerc [5], Simon Ville [6], Claire Pouteil-Noble [7], Jean-Philippe Coindre [8], Moglie Le Quintrec [9], Eric Rondeau [10], Olivia Boyer [11], François Provôt [12], Djamal Djeddi [13], W Hanf [14], Yahsou Delmas [15], Ferielle Louillet [16], Annie Lahoche [17], Guillaume Favre [18], Valérie Chatelet [19], Emma Allain-Launay [6], Claire Presne [20], Ariane Zaloszyc [21], Sophie Caillard [21], Stéphane Bally [22], Quentin Raimbourg [23], Leila Tricot [24], Christiane Mousson [25], Aurélie Le Thuaut [26], Chantal Loirat [27], Veronique Fremeaux-Bacchi [28]

blood

PHRC STOPECU

Caractéristiques génétiques

	Age < 18 years (n=19)*	Age ≥ 18 years (n=36)	All (n=55)
Female/male	7 (37%)/12(63%)	17(47%)/19(53%)	24(44%)/31(56%)
Complement gene variants	8 (42%)	20 (55%)	28 (51%)
Complement factor H	1 (5%)	5 (14%)	6 (11%)
Membrane-cofactor protein	5 (26%)**	7 (19%)	12 (22%)
Complement factor I	0 (0%)	6 (17%)	6 (11%)
C3	0 (0%)	2 (6%)	2 (5%)
Combined	2 (11%)	0 (3%)	2 (4%)
No variant/ Positive *anti-factor H antibodies*	4 (21%)	0 (0%)	4 (7%)
No variant / No anti-Factor H antibodies	7 (37%)	16 (44%)	23 (42%)
> 1 aHUS episode before inclusion in the study***	4 (21%)	4 (11%)	9 (16%)
At aHUS onset**			
Serum creatinine (µmol/)	361 [54;1920][a]	454 [91;1660][b]	421 [54 ;1920]
Requirement for dialysis	8 (42%)[a]	16 (44%)[a]	24 (43%)
Extra-renal manifestations	10 (52%)	14 (40%)	24 (43%)[c]
Neurological manifestations	4 (21%)	7 (20%)	11 (20%)
Cardiac manifestations	6 (31.5%)	4 (11%)	10 (18.5%)
Others	6 (31.5%)[α]	8 (23%)[β]	14 (25%)

STOPECU: Etude prospective: Résultats

- Rechutes en 24 mois: 13 patients sur 55

- Facteurs de risque de rechute:

→Présence d'un variant OR 16,20 (0 rechute en l'absence de variant)

→Sexe féminin OR 4,21

→Concentration de C5b-9 > 300 ng/mL

→Besoin EER dernier épisode SHUa avant inclusion OR 0,17

Fakhouri, F, Blood, 2020

Treatment strategy with ravulizumab ?

- Chronic treatment +++
  - after evidence of eculizumab effect (switch)
  - if recurrence after eculizumab discontinuation
- Acute treatment ?
  - Certainty of diagnosis:
    - Familial form
    - Classical post partum aHUS
  - Renal transplantation with a risk of recurrence of aHUS

Treatment strategy for aHUS after an initial phase of PE?

- Initial treatment at the acute phase: eculizumab or ravulizumab for at least 6 months
- At 6 month (or 12 month):
  - If on chronic dialysis, and no hematological sign of TMA: stop anti-C5 therapy (low risk of recurrence)
  - If off dialysis, and no further sign of TMA or improvement in renal function, careful stop anti-C5 therapy (significant risk of recurrence according to genetic variants)
- Treatment of recurrence: ravulizumab versus eculizumab
- Chronic treatment with eculizumab: stop or switch to ravulizumab (native kidneys, or renal grafts)