Webinars

Thrombotic Microangiopathies

Hemolytic uremic syndrome and other thrombotic microangiopathies

EuroBloodNet Topic on Focus

Management of atypical HUS

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Network Hematological Diseases (ERN EuroBloodNet)

Lecture Fees:

Alexion, Sanofi-Genzyme, Ablynx, Berlin Chemie, Novartis, Astra Zeneca, Boehringer Ingelheim, Santis, Bayer, Lilly

Consultant Fees:

Alexion, Ablynx, Sanofi-Genzyme, Astra Zeneca, Boehringer Ingelheim, Bayer

Travel Support:

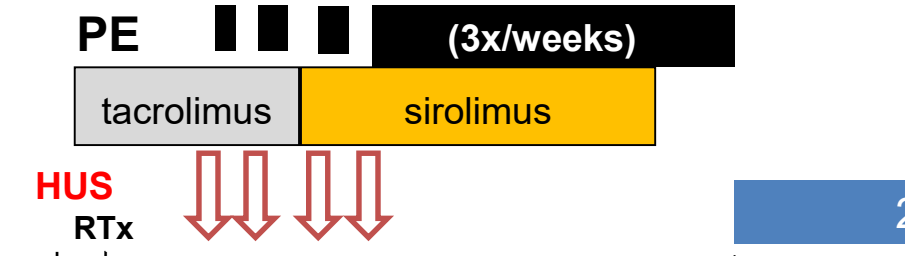
Alexion

Webinar rules

- **30-35min presentation + 15 min Q&A session**
- **Microphones will be muted by host to avoid back noise**
- **Please, stop your video to improve internet conexion**
- **Send your questions during the presentation through the chat**

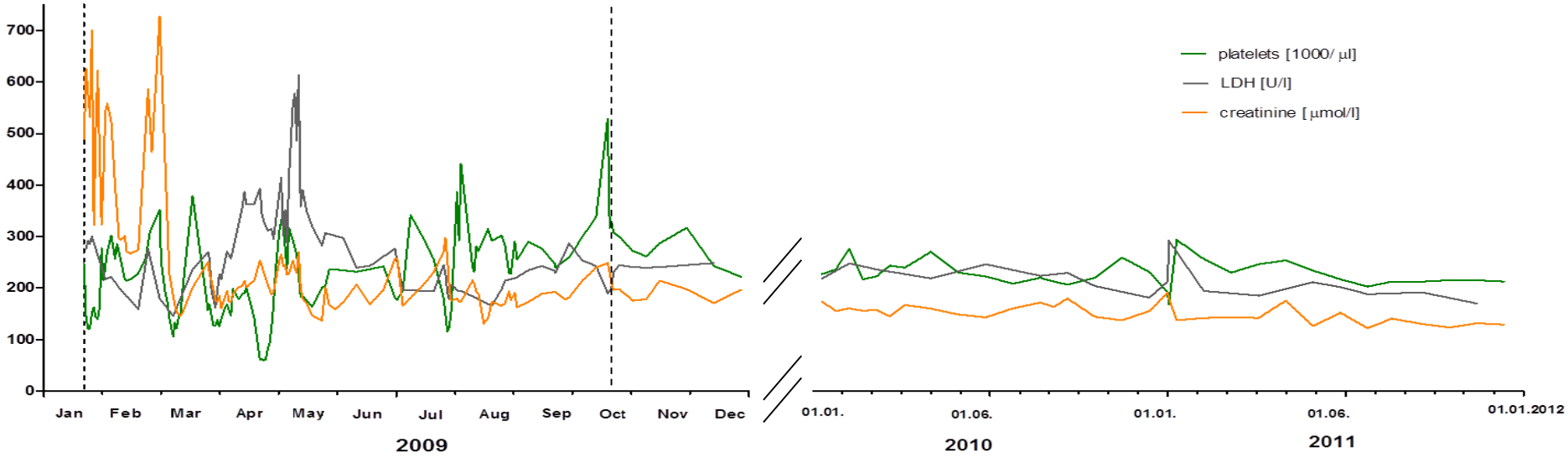
1. **Personal experience – Learning from Individual cases**
2. **Ravulizumab – a new treatment option**
3. **Discontinuation Strategy**

Pat. with 4. kidney transplant. No mutation detected. Treatment with eculizumab since 9/2009



Eculizumab (Soliris®)
Initial 4 x 900 mg, than 1200mg every 2 weeks

2 x 500 mg MMF and 7.5 mg prednisolone



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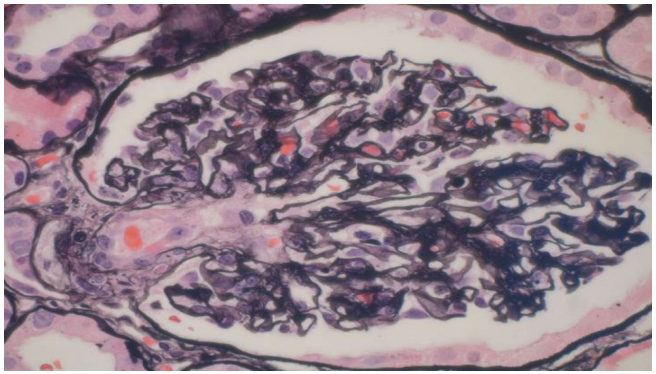
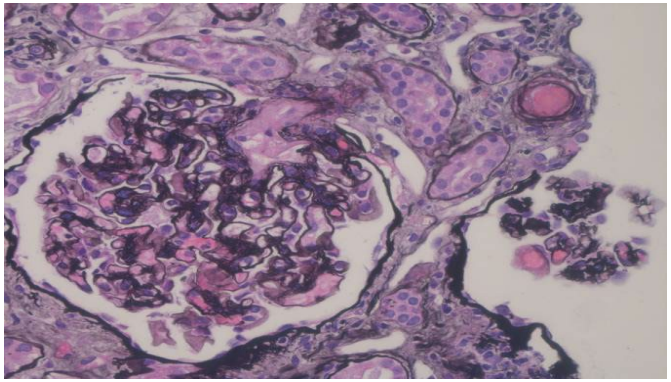
Histological TMA lesions can resolve and relapse quickly

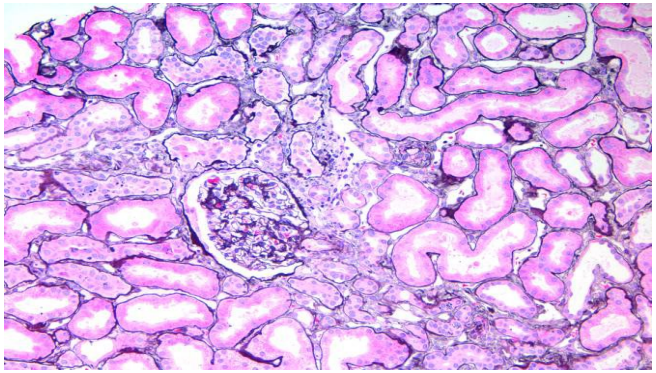
3.3.2009



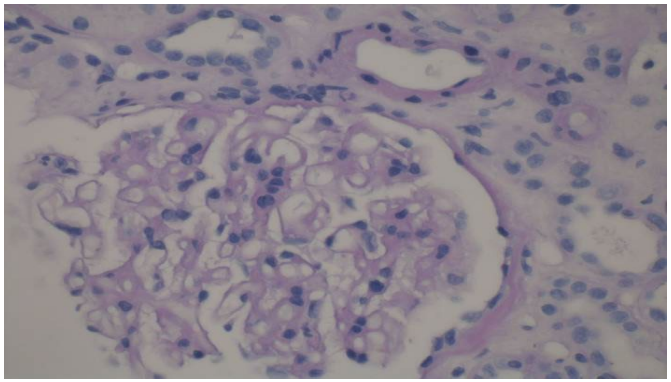
27.3.2009



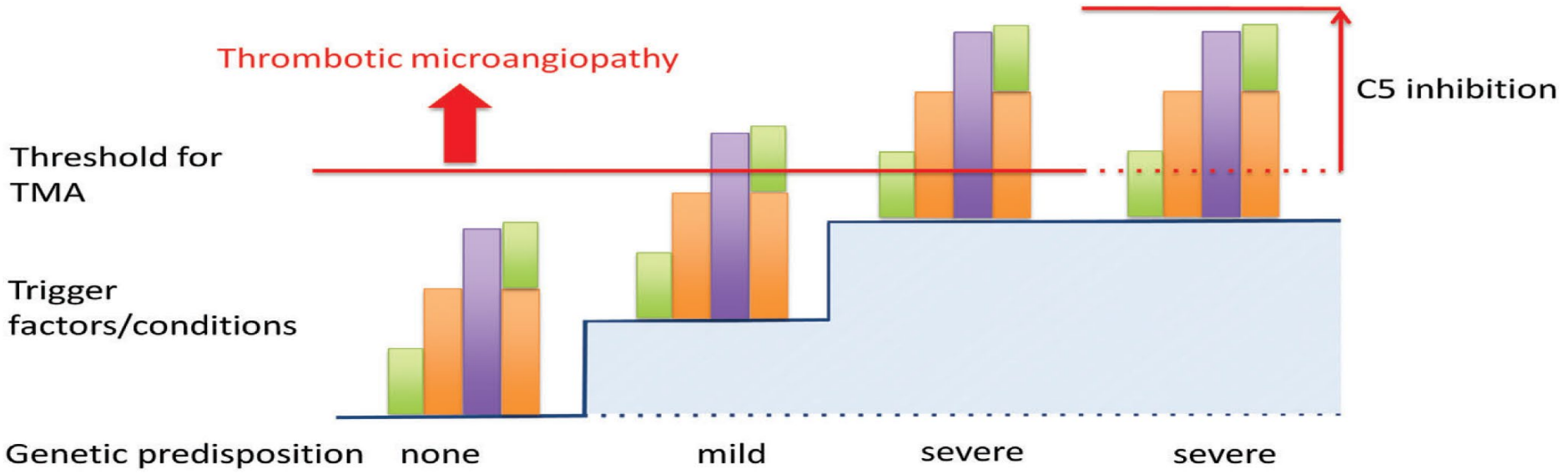
11.3.2009



15.4.2009

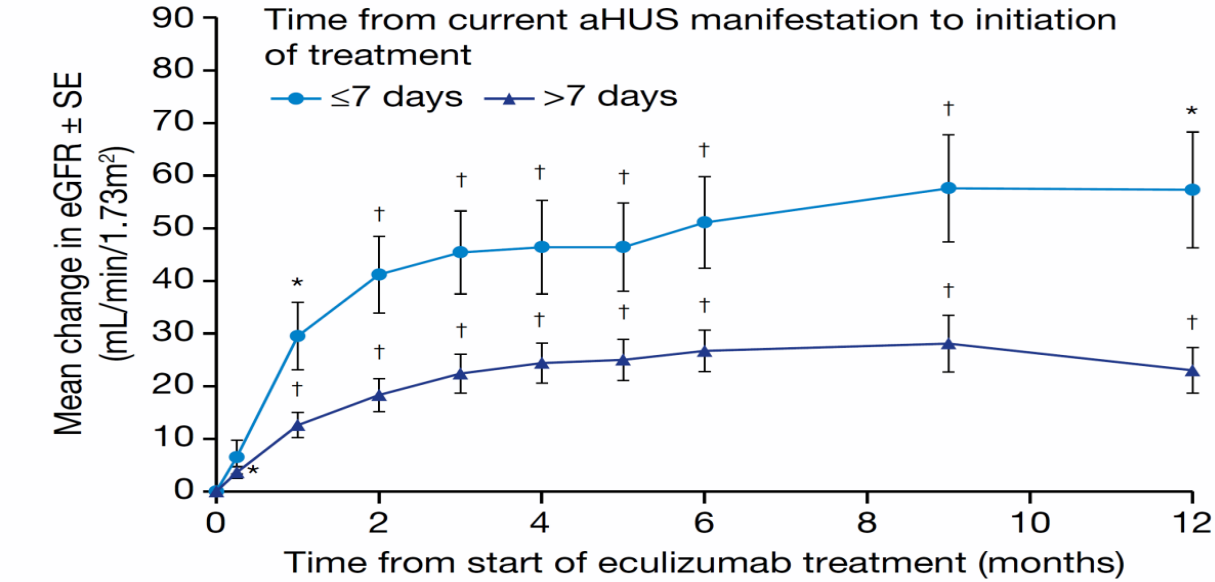


An „C5 inhibitor perspective“ on the second hit model or secondary aHUS forms



Riedl et al.., Semin Thromb Hemost; 40:444–464. 2014.

Early Initiation of eculizumab improves long-term outcome



*P<0.001 and †P<0.0001 vs baseline

Vande Walle et al, ISICEM 2015

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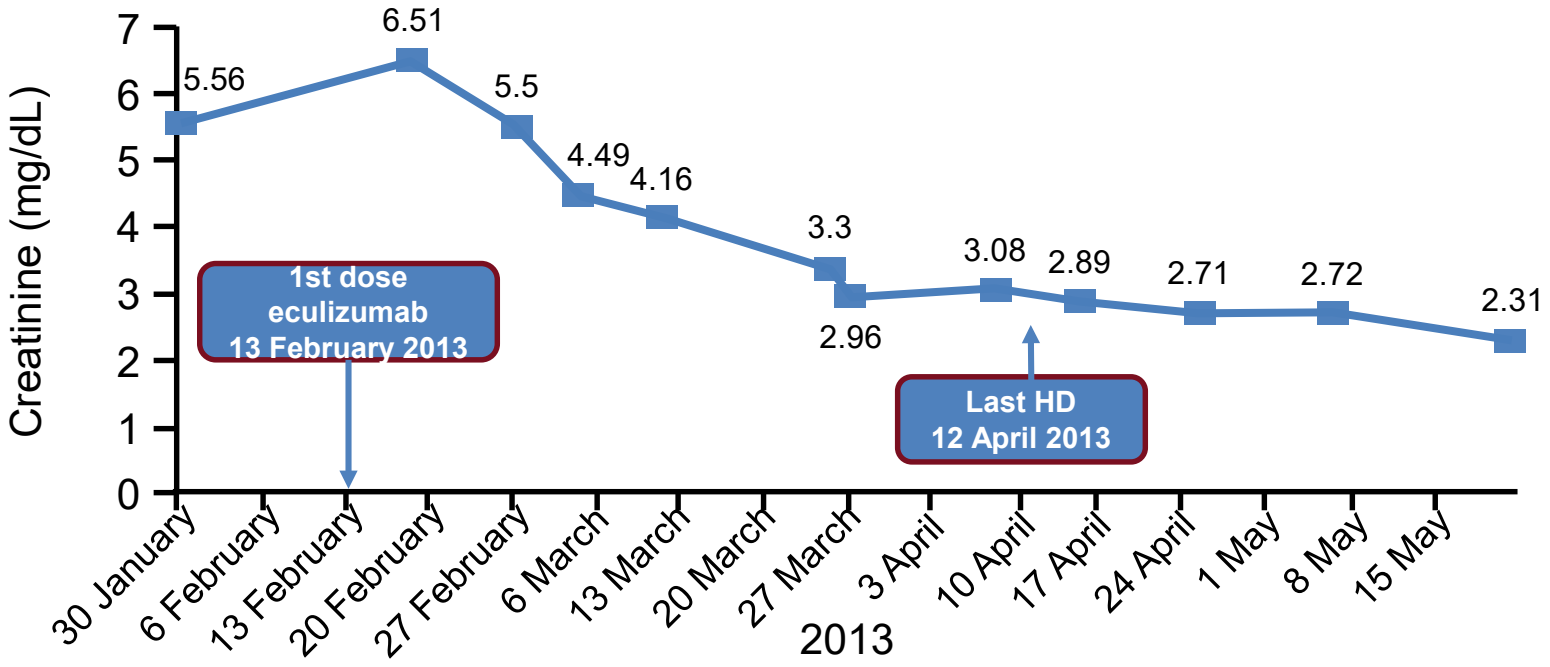
39 y. old woman, HUS 8/12, malignant nephrosclerosis, after 6 month on HD start with eculizumab



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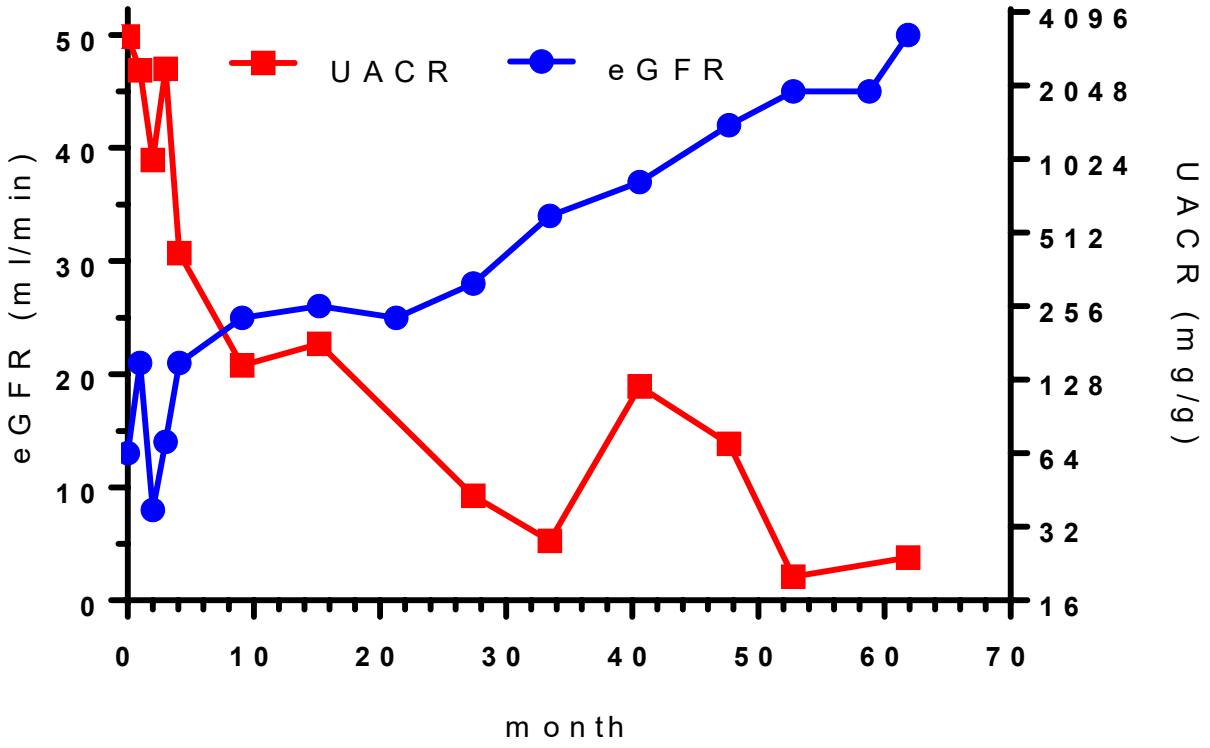
female patient, born 1981, familiar HUS,

- 6/2013 HUS with acute hemodialysis for 5 days, 2x PE, than eculizumab for 4 weeks
- Father had HUS, died after 7 years of hemodialysis
- 8/2013 recurrence, creatinine: 440 µmol/l, platelets 56/nl, LDH 957 U/l, Hb 8,5 g/dl
- 11/2013 shortness of breath (NYHA III), ejection fraction 32%; reduced eculizumab dosage to once weekly for 2 doses with recovery
- Genetics: CFI Mutation c.191C>T (p.Pro64Leu),

Kidney function is still improving after 5 years of treatment



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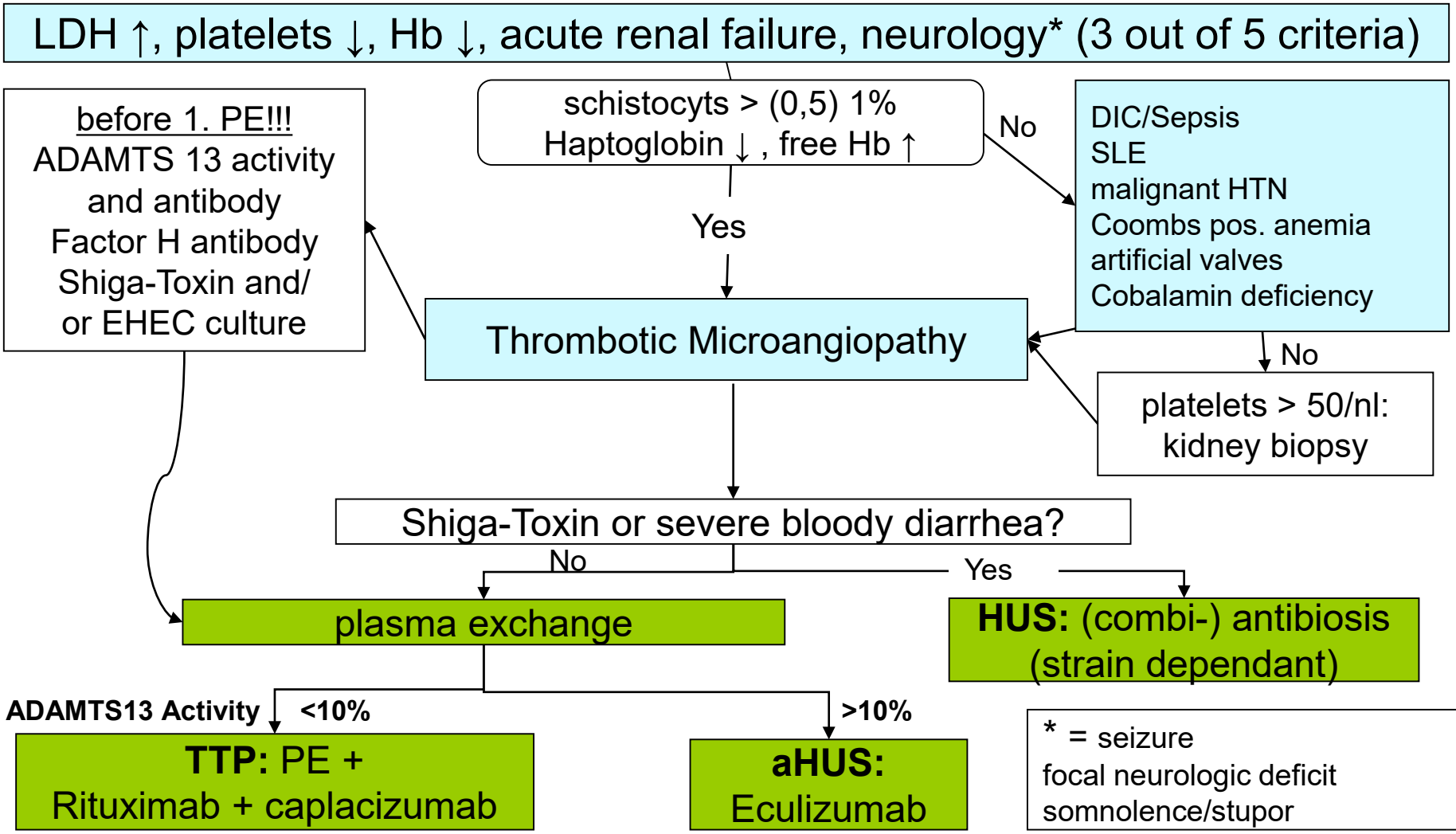
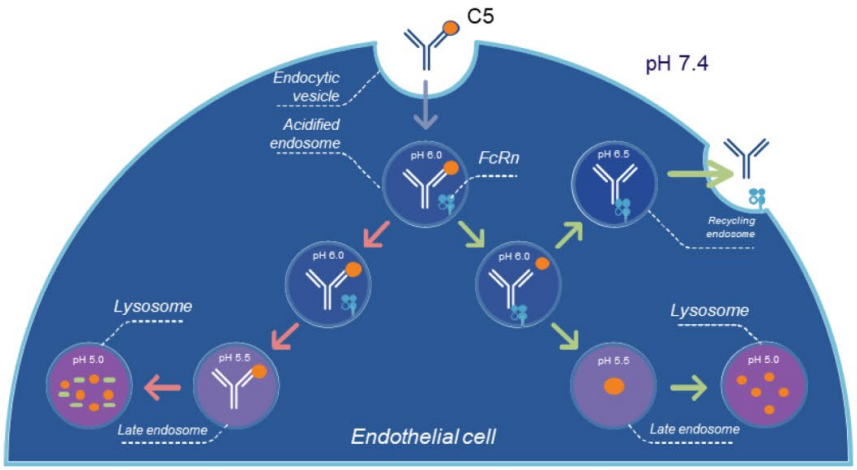

LDH ↑, platelets ↓, Hb ↓, acute renal failure, neurology* (3 out of 5 criteria)
schistocyts > (0,5) 1%
Haptoglobin ↓ , free Hb ↑
No
Yes
DIC/Sepsis
SLE
malignant HTN
Coombs pos. anemia
artificial valves
Cobalamin deficiency
before 1. PE!!!
ADAMTS 13 activity
and antibody
Factor H antibody
Shiga-Toxin and/
or EHEC culture
Thrombotic Microangiopathy
No
platelets > 50/nl:
kidney biopsy
Shiga-Toxin or severe bloody diarrhea?
No
Yes
plasma exchange
HUS: (combi-) antibiosis
(strain dependant)
ADAMTS13 Activity
<10%
>10%
TTP: PE +
Rituximab + caplacizumab
aHUS:
Eculizumab
* = seizure
focal neurologic deficit
somnolence/stupor

Ravulizumab

Ravulizumab provides pH-dependant elimination of C5



→ *Eculizumab: no dissociation of C5*

→ *Ravulizumab: pH-dependent dissociation of C5*

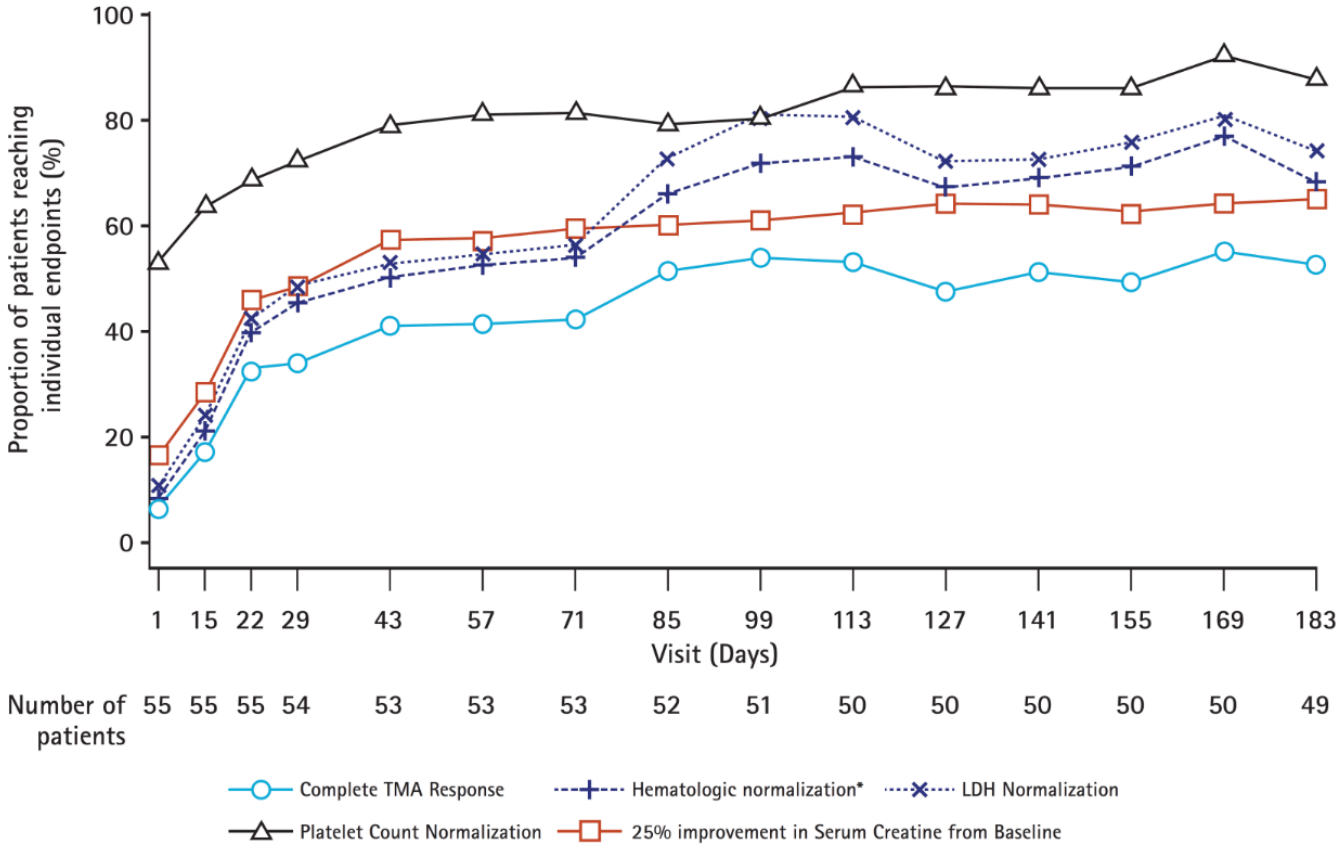
- **Ravulizumab binds to the same C5 epitope as eculizumab[1,2]**
  - Inhibits cleavage to C5a and C5b, preventing the formation of the terminal complement complex
- **FcRn salvage pathway is a protective mechanism to maintain circulating immunoglobin (Ig)G levels[3,4]**
  - FcRn binds to IgG with pH-dependent affinity
  - At low pH in the early endosome, IgG binds to FcRn and is sorted to the cell surface (rather than delivered to the lysosome)
  - FcRn does not bind IgG at pH 7.4, and IgG is released back into extracellular fluid
- **Modifications in 4 amino acids to increase half-life via:[1]**
  - release of C5 in the endosome at pH 6.0
  - increased affinity for FcRn receptor at pH 6.0

1. Sheridan D, et al. *PLoS One*. 2018;13(4):e0195909; 2. Rother RP, et al. *Nat Biotechnol*. 2007;25(11):1256-1264 3. Ryman J, Meibohm B. CPT Pharmacometrics Syst Pharmacol. 2017;6(9):576-588. 4. Devanaboyina S, et al. MAbs. 2013;5(6):851-859

		Ravulizumab		Eculizumab[1]	
		Start (once)	Duration (alle 8 Wo. ab Tag 14)	Start (4 weeks)	Duration (every 2 weeks, Day >35)
Dosing	5-10 kg	600 mg	300 mg	300 mg	300 mg
	10-20 kg	600 mg	600 mg	600 mg	300 mg
	20-30 kg	900 mg	2100 mg	2 x 600 mg	600 mg
	30-40 kg	1200 mg	2700 mg	2 x 600 mg	900 mg
	40-60 kg	2400 mg	3000 mg	900 mg	1200 mg
	60-100 kg	2700 mg	3300 mg		
	>100 kg	3000 mg	3600 mg		
Costs (Germany)	300 mg vial	5.695 €		5.880 €	
	Costs per year	407.193 €		611.520 €	
Monitoring	Messverfahren	free C5		CH50	

modified from Menne, Nephro-News 15: 2/21

Complete TMA response components over time



Rondeau et al., Kidney Int. 2020;97:1287-1296

Comparison of Ravulizumab and Eculizumab outcome data

	Current study: 311 (NCT02949128)	C10-004 (NCT01194973)[6]	C08-002 (NCT00844545, NCT00844844)[8]	C08-003 (NCT00838513, NCT00844428)[8]
Patient demographics				
Description of study population	Patients with aHUS naïve to complement inhibitor treatment	Patients with aHUS	Patients with aHUS and progressing TMA	Patients with long duration of aHUS and CKD
Study drug	Ravulizumab	Eculizumab	Eculizumab	Eculizumab
Total number of patients	56	41	17	20
Number of adolescent patients below 18 years of age	0	0	1	5
Patient outcomes (by 26 weeks)				
Complete TMA response,[d] n (%) 95% CI	30 (54) 40–68	23 (56) 40–72	11 (65) 38–86	5 (25) 9–49
Hematologic normalization,[e] n (%)	41 (73)	36 (88)	13 (76)	18 (90)
Platelet count normalization, n (%)	47 (84)	40 (98)	14 (82)	NA
LDH normalization, n (%)	43 (77)	37 (90)	14 (82)	19 (95)
eGFR increase, mean	35 ± 35	29 ± 24	32 (14–49)	6 (3–9)
Improvement in eGFR category of at least 1 stage, n (%)	32 (68)	26 (63)	10 (59)	7 (35)
Death, n/N	3/56	0/41	0/17	0/20

Rondeau et al., Kidney Int. 2020;97:1287-1296

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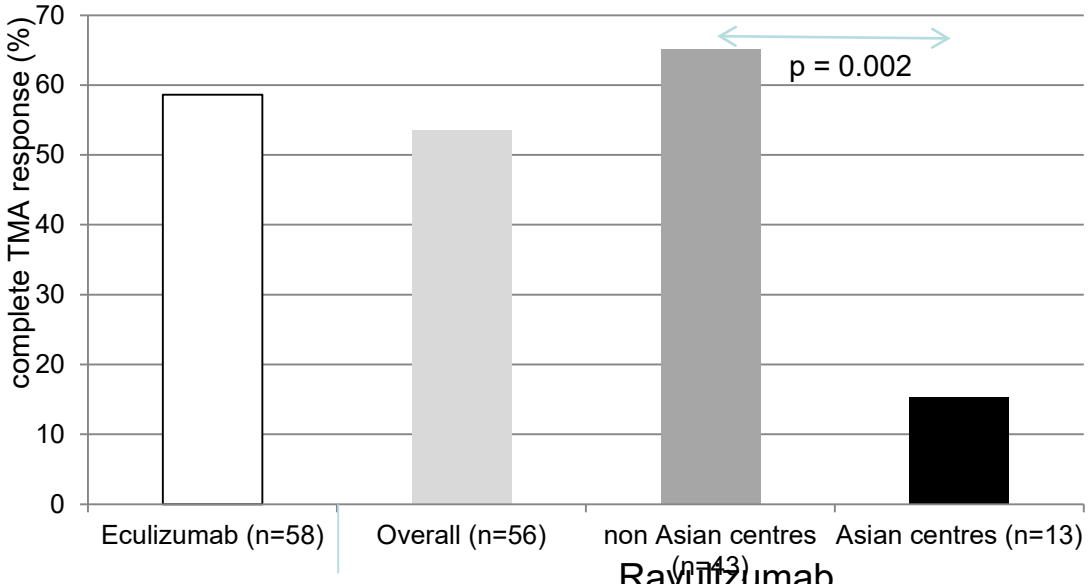
Patients in Asian centres responded „quite“ poorly probably due to health care differences



- 10 out of 13 patients in Asian centres were started after day 28, no compl. TMA response
- 3 patients were started prior to day 28, 2 had a complete TMA response (66,7%)
- In non Asian centres all patients were started prior to day 28

Menne et al., Kidney Int. 2020;97:1106-1108

Overview of aHUS treatment discontinuation
–
clinical experiences and good practices in aHUS

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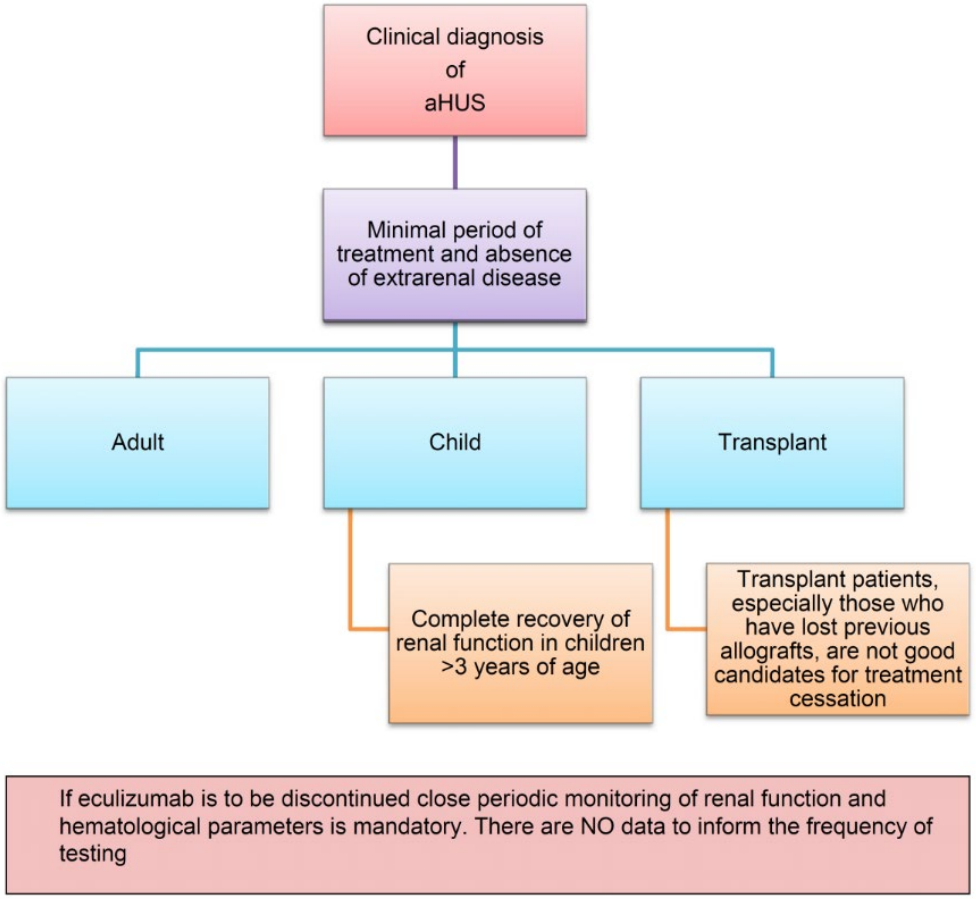
KDIGO Controversy Conference

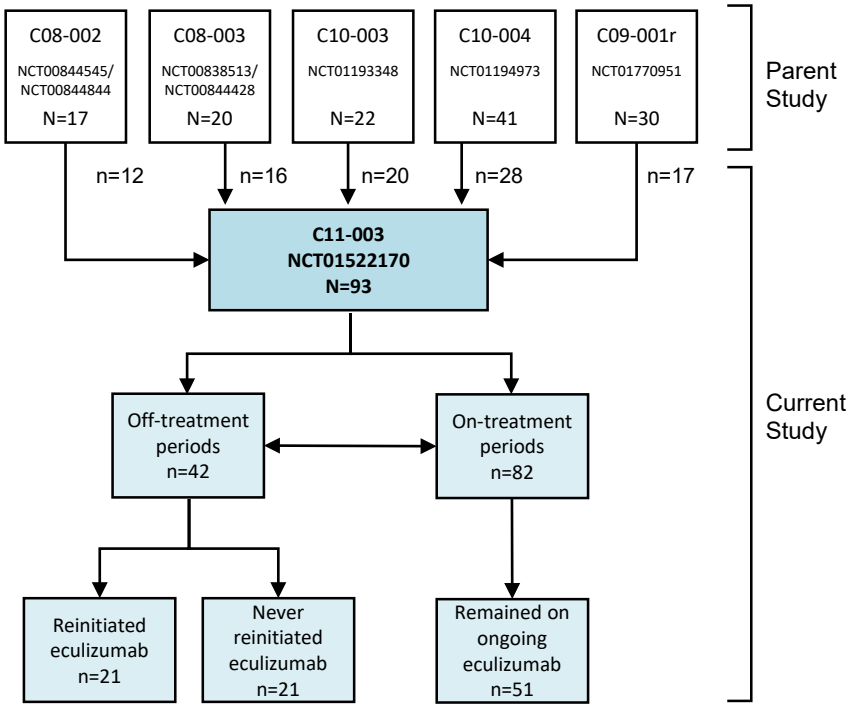
Discontinuation?



- individual decision
- Duration at least 6 months
- 3 months stable kidney function
- on dialysis for 4-6 months

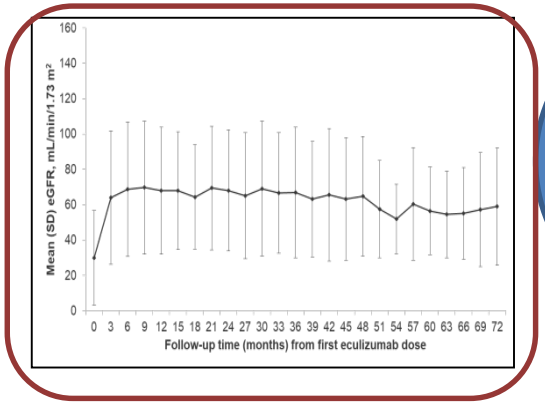
Goodship et al., Kidney International (2017) 91, 539–551

Patient Disposition And Overall Study Design



- Study visits every 3 months
- Patients from the original 5 trials that enrolled in the long-term study (current study)
  - Some patients lost to follow-up and/or death
  - Some patients could not enroll in current study due to regulatory considerations
- Followed prospectively from enrollment in current study and retrospectively from parent trial close, to enrollment
- Treatment regimen in follow-up as per treating physician

Menne et al., BMC Nephrol. 2019 Apr 10;20(1):125



Renal improvement sustained over 6 years without reduced effect

Longest ever follow-up of patients on eculizumab

Efficacy and safety profile confirmed

What are the key messages?

Describes characteristics of patients that discontinue

Population that had reached an almost normal renal function

Closely monitored for signs of TMA, and quickly restarted if needed

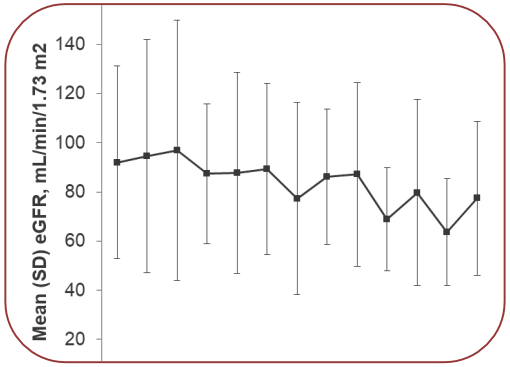
Confirmed TMA rate is increased in patients that discontinued treatment

13.5-fold increase in TMA rate

Pediatric aHUS onset

Identified complement abnormalities

History of multiple TMAs



Menne et al., BMC Nephrol. 2019 Apr 10;20(1):125

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Our recommendation!

RESEARCH ARTICLE Open Access

Outcomes in patients with atypical hemolytic uremic syndrome treated with eculizumab in a long-term observational study

Jan Menne[1*], Yahsou Delmas[2], Fadi Fakhouri[3], Christoph Licht[4], Åsa Lommelé[5], Enrico E. Minetti[6], François Provôt[7], Eric Rondeau[8,9], Neil S. Sheerin[10], Jimmy Wang[11], Laurent E. Weekers[12] and Larry A. Greenbaum[13]

Conclusions: The current study confirms the efficacy and safety of eculizumab in aHUS, particularly with regard to long-term renal function and TMA events. Pediatric age at disease onset and presence of genetic or autoimmune complement abnormalities are risk factors for TMA events off treatment. Overall, patients who discontinue eculizumab may be at risk for additional TMA manifestations and renal function decreases. Discontinuation of eculizumab, with careful monitoring, is an option in select patients with consideration of patient preference, organ function normalization, and risk factors for relapse, including mutational analysis, age of onset, and history of multiple TMA episodes.

Menne et al., BMC Nephrol. 2019 Apr 10;20(1):125

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Stopping of C5 inhibitor is relatively save in patients without a rare variant

	Ardissino et al (2014)[11]	Fakhouri et al (2016)[12]	Wijnsma et al (2017)[13]	Merrill et al (2017)[17]	Present study	Total
Patients with complement gene screening (n)	16	38	18[b]	13[c]	55	140
Adults/children	8/8	29/9	14/4	13/0	36/19	100/40
Duration of follow-up[a] (range)	13.1 months (0.4-40)*	22 months (5-43)*	NS	239 days (0-1390)*	19.8 (5.4-24)**	
Patients with no variant and no anti-FH Ab (n)	5	16	4	8[d]	23	56
Relapse rate (%)	0	0	0	1 (13%)	1 (4%)	2 (3.5%)[e]
Patients with rare variants (MAF<0.1%)	7	21	13	5	28	74
Relapse rate (%)	3 (43%)	12 (57%)	5 (38%)	2 (40%)	12 (43%)	34 (46%)
Patients with rare pathogenic variants	4	18	9	2	26	59
Relapse rate (%)	3 (75%)	10 (56%)	3 (33%)	2 (100%)	10 (38%)	28 (47%)
Patients with CFH rare variants (P/LP variants (n), VUS (n))	2 (2, 0)	11 (9, 2)	7 (4, 3)	2 (1, 1)	6 (6, 0)	28 (22, 6)
Relapse rate (P/LP (n), VUS (n)) (%)	2 (2, 0)(100%)	8 (7, 1) (72%)	4 (2, 2) (57%)	1 (1, 0) (50%)	3 (3, 0) (50%)	18 (15,3) (64%)
Patients with MCP rare variants (P/LP (n), VUS(n))	2 (1, 1)	8 (7, 1)	0	2 (1,1)	12 (12, 0)	24
Relapse rate (P/LP (n), VUS (n)) (%)	0 (0, 0)	3 (3, 0) (37%)	-	0	6 (6, 0) (50%)	9 (9,0) (37%)
Patients with CFI rare variants (P/LP (n), VUS(n))	3 (1, 2)	2 (2, 0)	1 (0,1)	0	7 (6,1)	13
Relapse rate (P/LP (n), VUS (n)) (%)	1 (1, 0) (33%)	0 (0, 0)	0	-	2 (1, 1) (29%)	3 (2,1) (23%)
Patients with C3 rare variants (P/LP (n), VUS(n))	0	1 (0, 1)	4 (4, 0)	0	2 (2, 0)	7
Relapse rate (P/LP (n), VUS (n)) (%)		0	1 (1, 0) (25%)	-	0	1 (14%)
Patients with CFB rare variants (P/LP (n), VUS(n))	0	0	1 (1, 0)	1 (0, 1)	0	2
Relapse rate (P/LP (n), VUS (n)) (%)	-	-	0	1 (0, 1) (100%)		1 (0,1) (50%)
Patients with anti FH Ab	4[f]	1	1	0	4	10
Relapse rate	2 (50%)	0	0		0	2 (20%)

Without rare variant: 3,5%

With rare variant: 46%

Fakhouri et al, Blood 6;137(18):2438-2449

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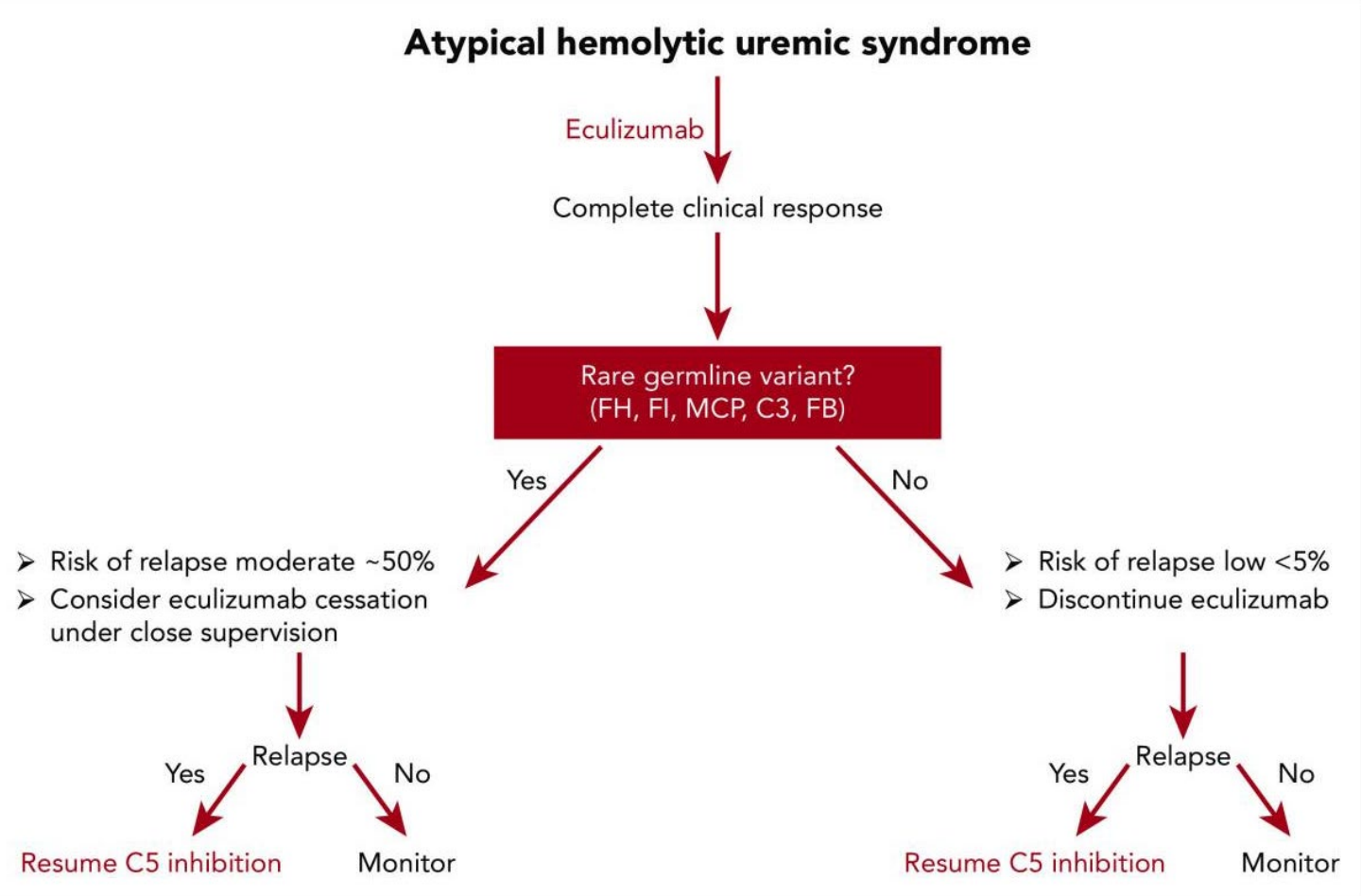
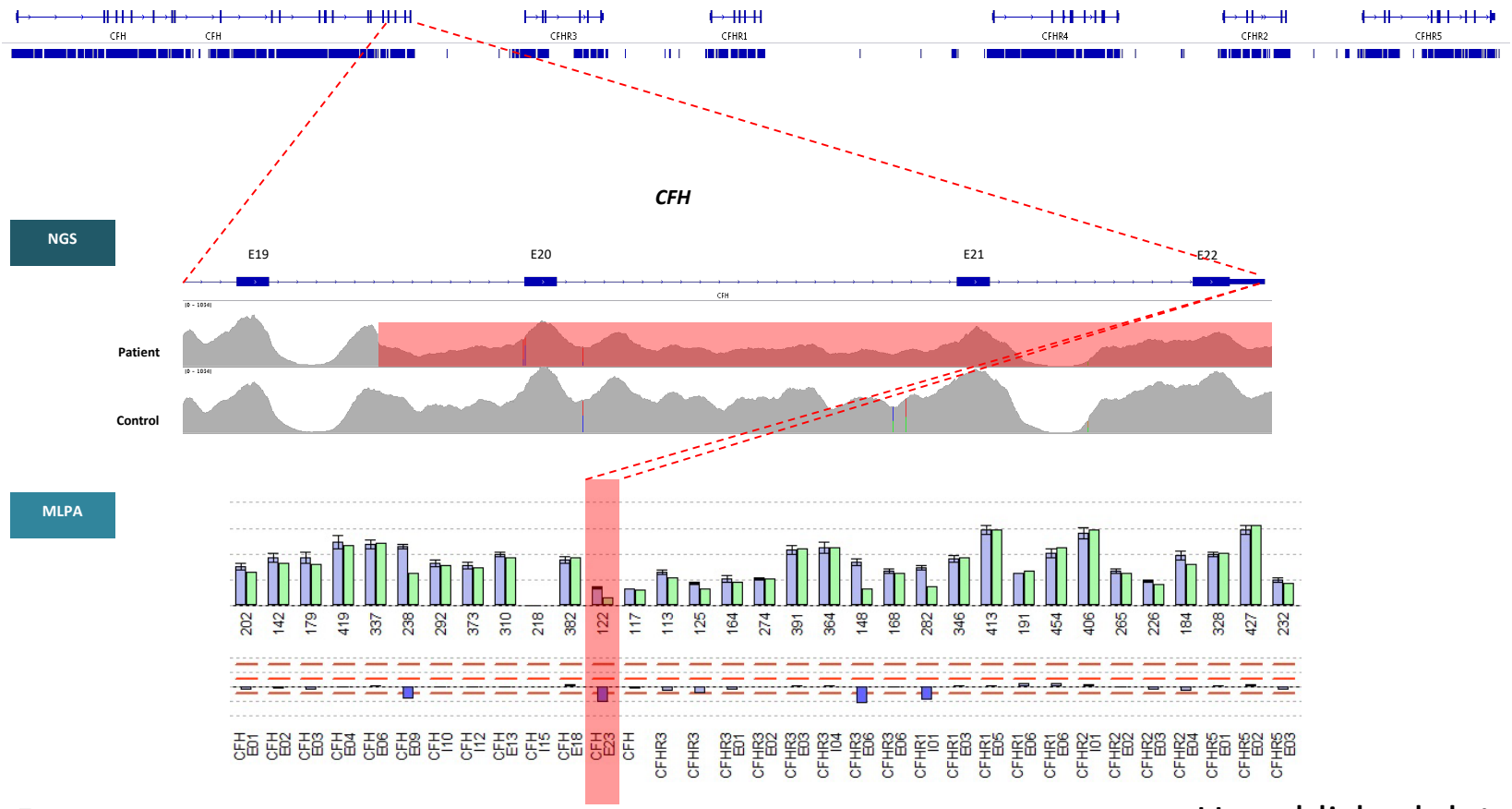
Treatment algorithm for discontinuation



Brodsky et al., Blood. 2021; 137(18): 2419–2420

Initial patient with 4. renal transplant: Only with NGS and MLP analysis mutation detected



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Unpublished data

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Can we stop eculizumab in some patients? Yes

The following patients are suitable candidates:

- Dialysis patient despite treatment with eculizumab for 2-3 months and no evidence on biopsy that the kidney can still recover
- patients without a mutation in a full genetic work-up and less than 2 aHUS relapses with a stable kidney function (GFR >20 ml/Min and UACR) for at least 2-3 months and no active extra renal aHUS manifestation
- Anti CFH antibody mediated aHUS in remission (no antibody detectable) after immunosupressive treatment
- uncertain diagnosis

After cessation of the drug the following parameters should be checked initially every 2 weeks: LDH, full blood count, creatinine, haptoglobin, UACR

What have I learned from treating >120 aHUS patients over the past 10 years?

- always check for Anti-CFH Antibody
- Even after long-term dialysis treatment, renal function can recover when C5 inhibition is started
- Do not wait too long before initiating C5 inhibition if the presence of aHUS is suspected
- TMA in a renal transplant might be a sign of aHUS even when humoral rejection is diagnosed
- C5 inhibition can lead to a substantial continuous improvement in renal function even after 1 year of treatment
- Many secondary TMA forms, including malignant hypertension, are complement mediated
- Even without a genetic mutation you can have severe relapsing aHUS

Discussion