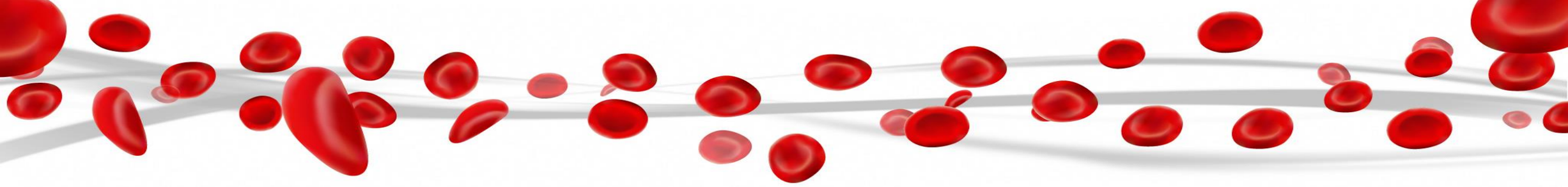

Webinars
Thrombotic Microangiopathies

Hemolytic uremic syndrome and other thrombotic microangiopathies

EuroBloodNet Topic on Focus

Drug-induced Thrombotic Microangiopathies

Speaker Dr Steven Grangé
Department of Nephrology
Rouen University Hospital
24th November 2021

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Conflicts of interests

Fees for board membership or symposia: Alexion, Octapharma, Sanofi

Travel support: Alexion, Octapharma, Sanofi

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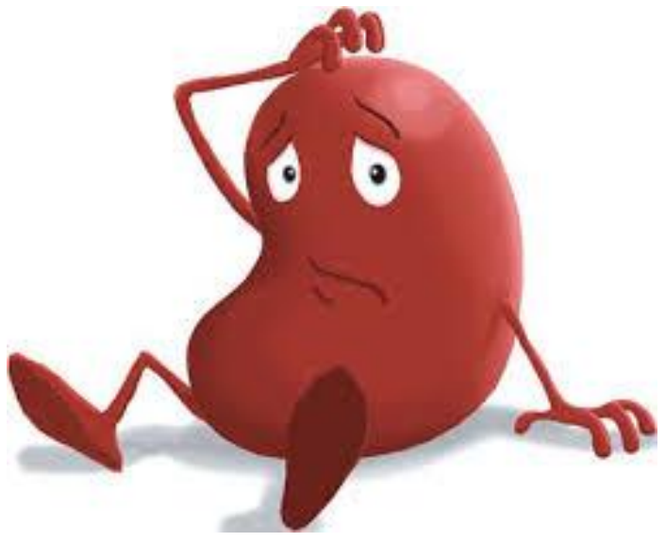
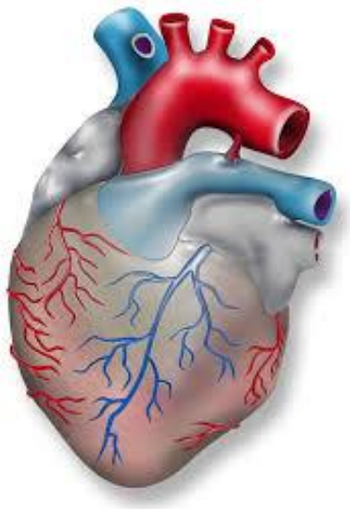
What is TMA?

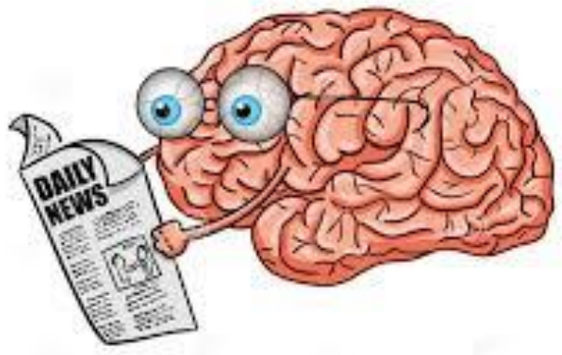
Microangiopathic hemolytic anemia

Peripheral thrombocytopenia

Organ failure of variable severity







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Etiology and outcomes of thrombotic microangiopathies

Retrospective study : 564 consecutive patients between 2009 et 2016
In 4 hospitals (CHU Tours)

Primary TMAs 6%

TTP 3%

aHUS 3%

Secondary TMAs 94%

35%

33%

26%

19%

UNDERDECLARED

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Bayer et al. CJASN 2019

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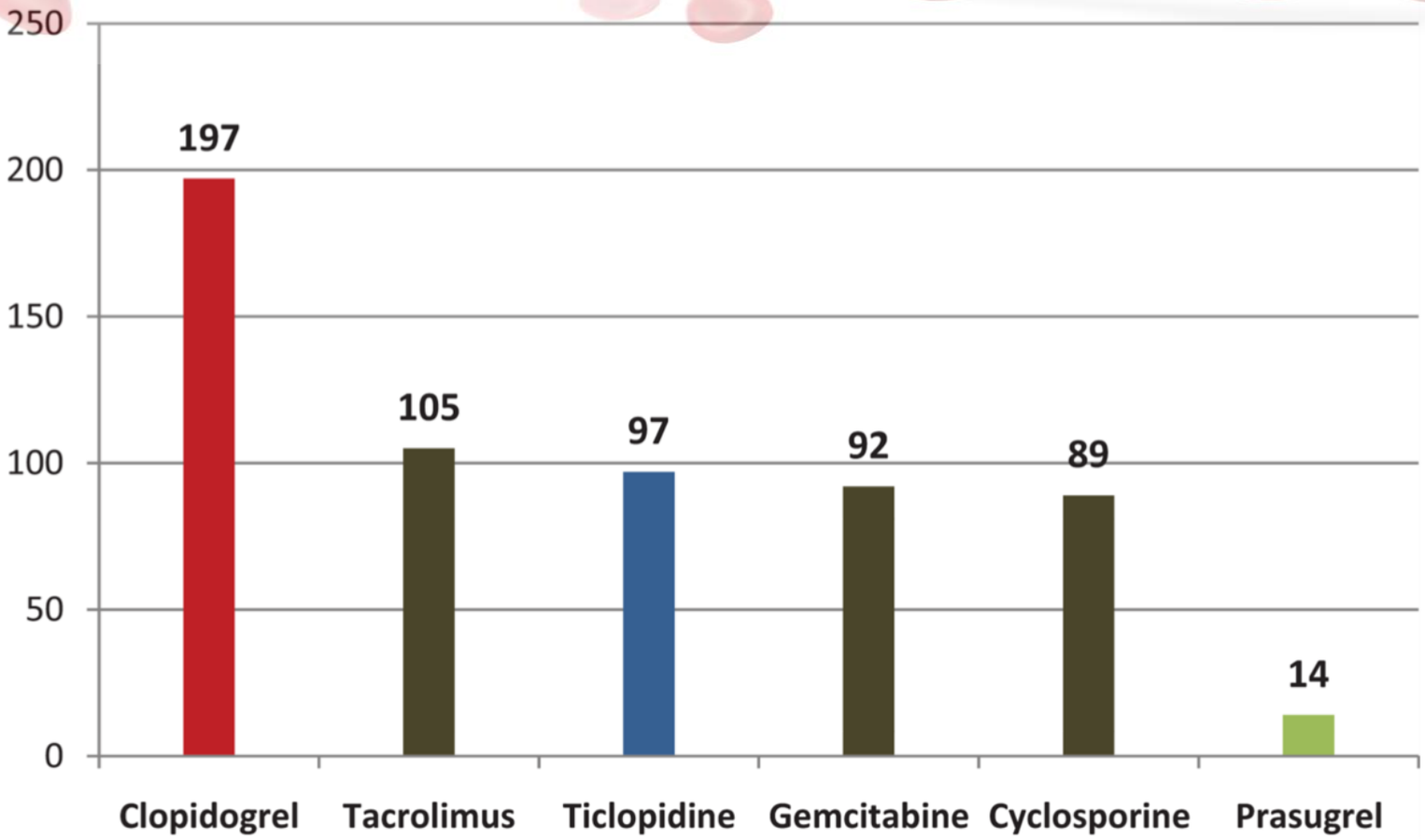
Epidemiology



Drugs and number of cases reported to FDA between 1998 and 2011

Ticlopidine: Incidence 0.01%, Low adamts 13 activity in 80% and anti adamts 13 antibodies 100%
(2-12 weeks) -> Plasmapheresis, no relapse

Clopidogrel: Incidence 0.001%, different mechanism, < 2 weeks

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Jacob et al. Semin Thromb Hemost 2012

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RESEARCH ARTICLE

Drug-induced thrombotic microangiopathy: Experience of the Oklahoma Registry and the BloodCenter of Wisconsin

Jessica A. Reese,[1] Daniel W. Bougie,[2] Brian R. Curtis,[2] Deirdra R Terrell,[1] Sara K. Vesely,[1] Richard H. Aster,[2] and James N. George[1,3]*

TABLE II. Reassessment of Oklahoma Registry Patients Who Had Been Previously Assigned to the Drug-induced Category

Drug	Total number of patients	Categories determined by re-assessment (number of patients)			
		Definite	Probable	Possible	Unlikely
Immune-mediated TMA					
Quinine[a]	25	19	1	5	–
Ticlopidine	2	–	–	2	–
Clopidogrel	1	–	–	1	–
Trimethoprim-sulfamethoxazole[b]	1	–	1	–	–
Alendronate[c]	1	–	–	1	–
Dose-dependent toxicity-mediated TMA					
Mitomycin	11	–	–	11	–
Cyclosporine	4	–	–	4	–
Tacrolimus	4	–	–	3	1
Gemcitabine	3	1	–	2	–
Carmustine	1	–	–	1	–
Cocaine[d]	1	–	–	1	–
Cytarabine	1	–	–	1	–
"Ecstasy"[e]	1	–	–	1	–
Pentostatin	1	1	–	–	–
Taxotere	1	–	–	1	–

1988-2014

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Reese et al. AJH 2015

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AJKD
Original Investigation

Quinine-Induced Thrombotic Microangiopathy: A Report of 19 Patients

Evaren E. Page, MPH,[1,2] Dustin J. Little, MD,[3] Sara K. Vesely, PhD,[1] and James N. George, MD[1,2]

19 patients from the Oklahoma Registry 1989-2015

18 with **quinine-dependent antibodies** reactive with platelets and/or neutrophils

18 women / 19 patients

Quinine exposure: Pill form for 18 patients and tonic water for 1

Abnormalities not characteristic of TTP: neutropenia, DIC, liver function abnormalities

17 of the 18 surviving patients required dialysis

14 developed CKD

Page et al. AJKD 2017

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How to distinguish antineoplastic drug-associated TMA from cancer-associated TMA

	Antineoplastic drug-associated TMA	Cancer-associated TMA
Wasting, weight loss, bone pain	0	+++
Hypertension	+++	0
Pulmonary symptoms	++	+
Renal insufficiency	++	±
ADAMTS13	Normal/detectable	Normal/detectable
Tear drop cells Erythroblasts	0	+++
DIC	0	++
Treatment	Stop chemo	Start chemo

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rangé, Coppo . Néphrologie et Thérapeutique 201

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Bone marrow exploration

Oberic et al., Oncologist 2009

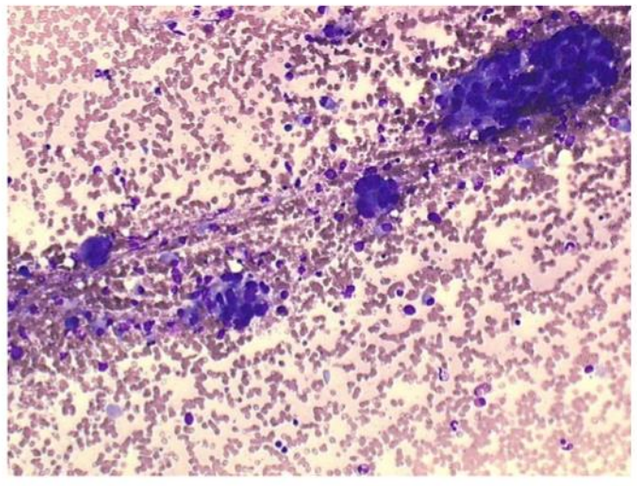
Table 3. Bone marrow aspiration and/or biopsy findings

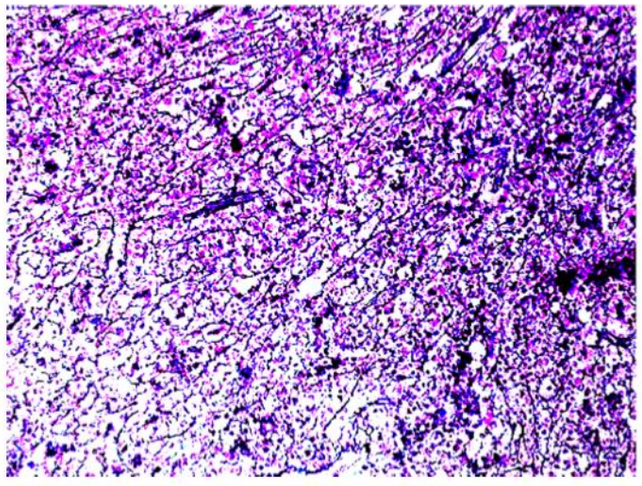
Patient no.	Results of bone marrow exploration
1	Erythroblastic hyperplasia
2	Metastatic cells; fibrosis
3	Metastatic cells
4	Metastatic cells
5	Metastatic cells
6	Metastatic cells
7	Metastatic cells
8	Erythroblastic hyperplasia
9	Metastatic cells; fibrosis
10	Metastatic cells
11	Erythroblastic hyperplasia
12	Metastatic cells; fibrosis
13	Metastatic cells; fibrosis
14	NA
15	NA
16	Metastatic cells
17	NA
18	NA
19	Metastatic cells
20	NA

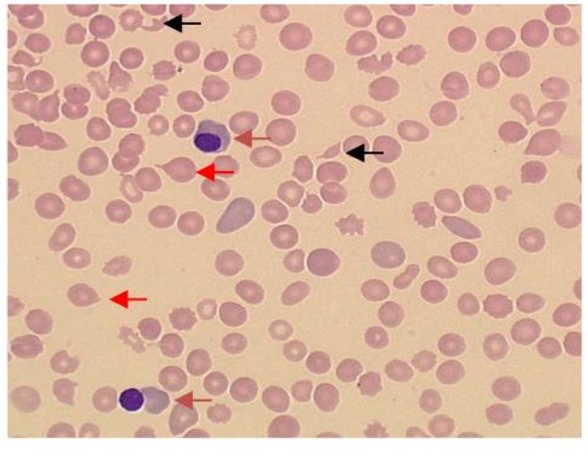
Abbreviation: NA, not available.

Bone marrow metastasis in 12/15 patients explored

Bone marrow fibrosis in 4 patients







- Schistocytes
- Tear drop cells
- Erythroblasts

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Mitomycin C-associated TMA

Medina et al., Curr Op Hematol 2001

Table 3. Clinical characteristics of patients with mitomycin C–associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome

	Lesesne [11]*	Snyder [21]*	Sheldon [12]*	Cantrell [17]*
Number of patients	85	55	39	12
Chemotherapy regimen included mitomycin C	99	93	82	100
Cumulative dose of mitomycin C >40 mg	99	NR	NR	100
Sex (% female)	59	78	59	58
Primary site of carcinoma				
gastric	26	9	44	50
breast	18	44	9	8
colorectal	16	22	20	8
Clinical features				
pulmonary	65	NR	49	100
neurologic	16	NR	18	25
Laboratory features				
microangiopathic hemolytic anemia	100	95	90	100
thrombocytopenia	100	78	92	100
renal failure	100	78	92	100
Death	74	55	72	83

*All values except number of patients are percentages.
NR, not recorded.

TMA in 2% to 15% of patients receiving MMC

Clinical features typically occur 4 to 8 weeks after the last MMC infusion

Usual cumulated dose > 40 mg

Lung involvement is a frequent feature+++

- Dyspnea

- Lung oedema

- Respiratory distress

Renal failure if cumulated dose > 50-70 mg

ADAMTS13: normal or mildly decreased

Diffuse endothelial lesions induced by the drug

Poor response to plasma exchange ± immunoadsorption

Poor prognosis; death at ~ 4 months

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Paul Coppo's slide

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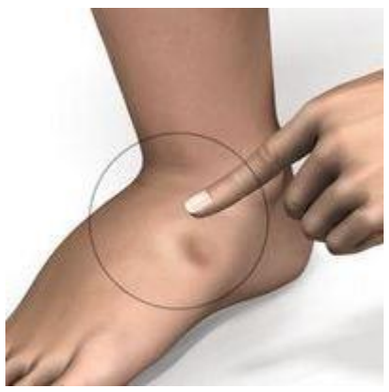
GEMCITABINE-induced TMAs

Retrospective study, 1998-2015
French Pharmacovigilance network + French TMA Reference Center + Complement Alternative Pathway Registry HEGP VFB

n = 120

210 days of treatment (median)

Cumulative dose of 13 g/m2



57%

62%

Daviet et al. British Journal of Clinical Pharmacology 2019

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GEMCITABINE-induced TMAs

		Patients (n = 120)
Type of treatment	Cessation of gemcitabine	100% (52/52)
	Anti-hypertensive treatment	57.4% (54/94)
	Plasma exchange	39.8% (39/98)
	FFP infusion	21.4% (21/98)
	Steroids	15.3% (15/98)
	Eculizumab	5.1% (5/98)
Response to treatment (n = 95)	Complete remission	42.1%
	Haematological remission only	23.1%
	Absence of remission	34.7%
Non-lethal serious adverse events	Haemorrhage	11.5% (9/77)
	Infection	11.5% (9/77)
Death		54.7% (29/52)
Main cause of death (n = 29)	Cancer evolution	34.5%
	TMA	65.5%

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aviet et al. British Journal of Clinical Pharmacology 201

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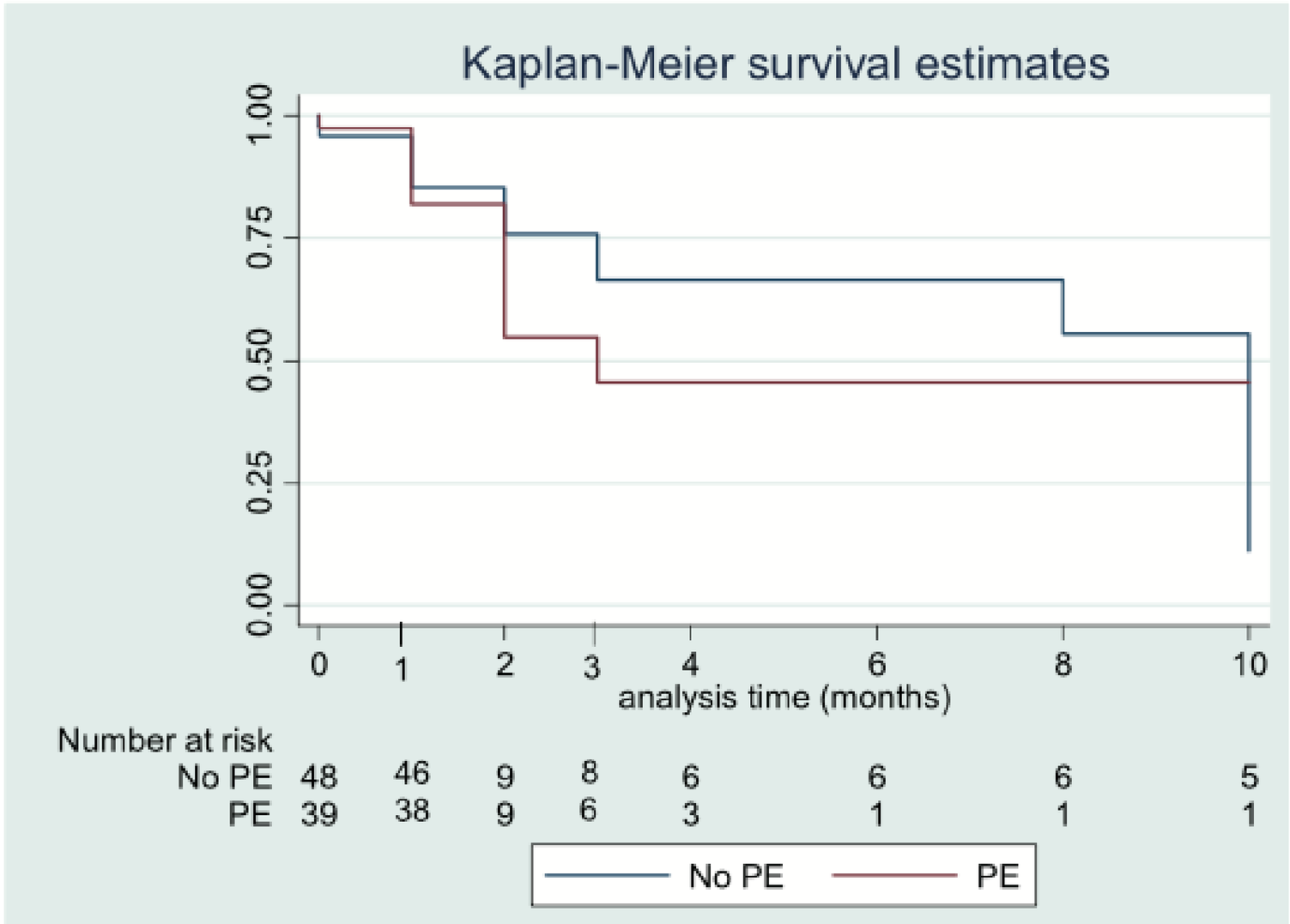
GEMCITABINE-induced TMAs



Renal characteristics	PE	No PE	
AKI	100% (39/39)	96.5% (56/58)	0.51
Creatinine at the time of diagnosis	297.5 (192.5–410)	162 (135–300)	0.0017
Missing	9 (23.1%)	14 (23.7%)	
Need for RRT	45.9% (17/37)	11.9% (7/59)	<0.001

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Daviet et al. British Journal of Clinical Pharmacology 2019

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Grall *et al. BMC Nephrology* (2021) 22:267
https://doi.org/10.1186/s12882-021-02470-3

BMC Nephrology

RESEARCH Open Access

Eculizumab in gemcitabine-induced thrombotic microangiopathy: experience of the French thrombotic microangiopathies reference centre

Maximilien Grall[1,2], Florence Daviet[3,2], Noémie Jourde Chiche[3,2], François Provot[4,2], Claire Presne[5,2], Jean-Philippe Coindre[6,2], Claire Pouteil-Noble[7,2], Alexandre Karras[8], Dominique Guerrot[9], Arnaud François[10], Ygal Benhamou[11,2], Agnès Veyradier[12,2], Véronique Frémeaux-Bacchi[13,2], Paul Coppo[14,2] and Steven Grangé[1,2*]

Co-funded by the Health Programme of the European Union

Objectives and methods

Describe clinical characteristics of patients and outcome of patients presenting a gemcitabine-induced TMA treated by eculizumab

Observational, retrospective, multicentric French study between 2011 and 2016

Inclusion criterion: gemcitabine-induced TMA treated by eculizumab

Exclusion criterion : TMA attributed to paraneoplastic TMA

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Grall, Grangé et al. BMC Nephrology 2021

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Baseline characteristics (1)

12 patients were included

AKI 100% (stage 3 KDIGO 58%), RRT 17%
Hypertension 92%, diffuse oedema 83%

Median time from gemcitabine initiation to occurrence: 6 months (range 1.7-16)

Cumulative dose: 27.5 g (range, 9.0-48)

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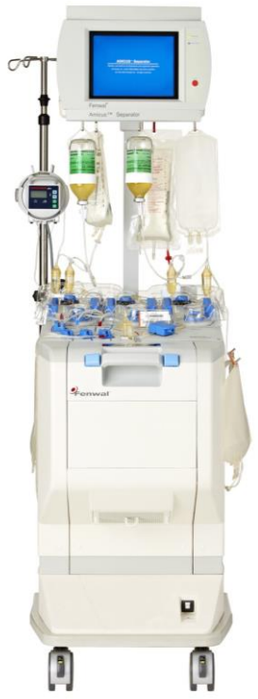
Treatment

- Eculizumab was started after a median of 15 days (range, 4-44)
- Median number of injections: 4 (range, 2-22)

- 5 patients had previously plasma exchanges with no or incomplete efficacy (median 7 PE; range, 4-9)



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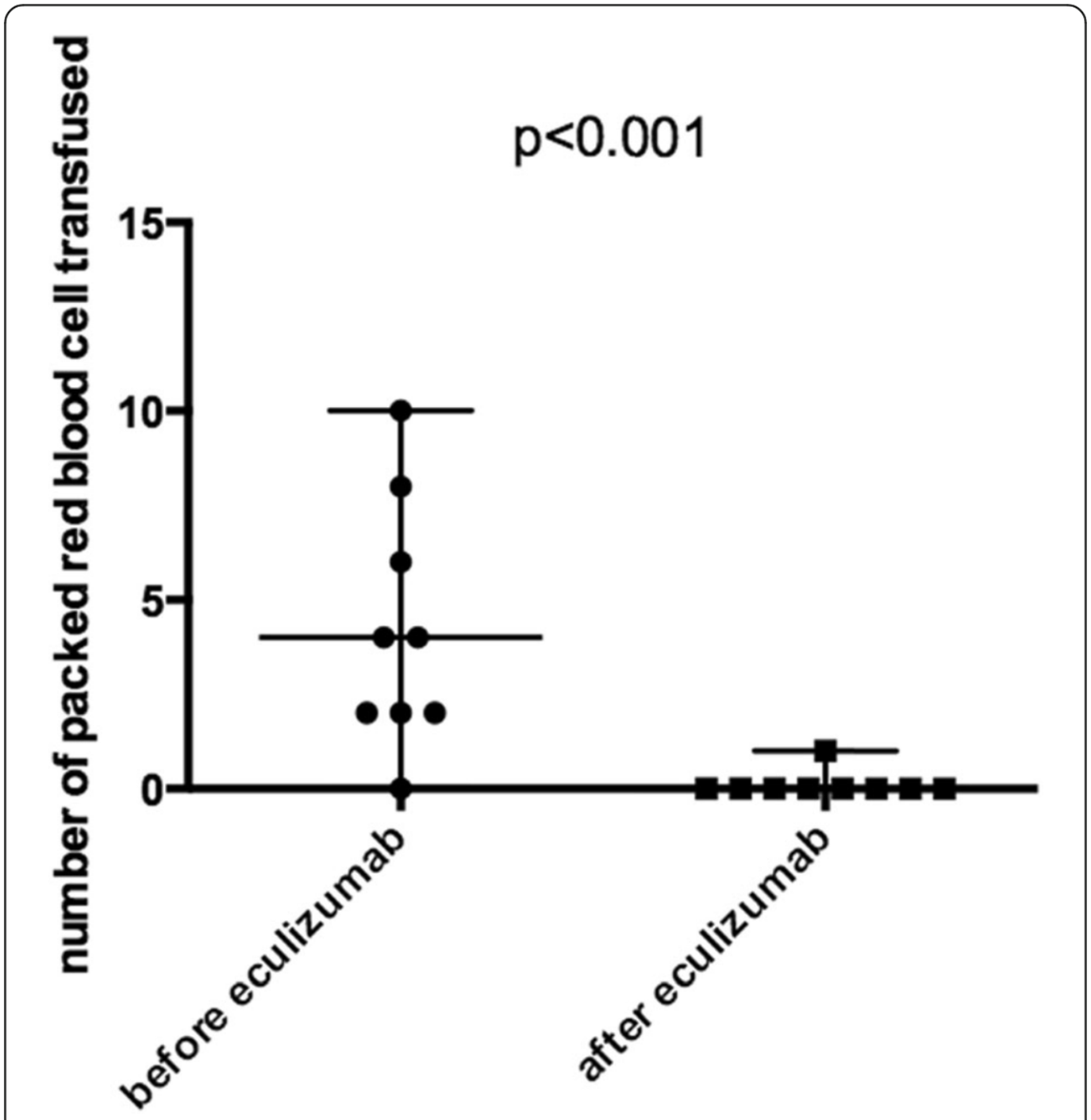

Fig. 2 Comparison of packed red blood cell transfusion before and after eculizumab therapy. Quantitative values are expressed as median with range

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Table 3 Outcome of patients

	Eculizumab group *N* = 12 (%)	**Control group *N* = 14 (%)**
Renal response	10 (83)	9 (64)
Partial	8 (66)	6 (43)
complete	2 (17)	3 (21)
eGFR at onset (ml/min/1.73m$^{2)}$	19 (0–76)	12 (0–31)
eGFR at the end of follow up	45 (0–119)	33 (0–66)

eGFR Estimated glomerular filtration rate. Quantitative values are expressed as median with range

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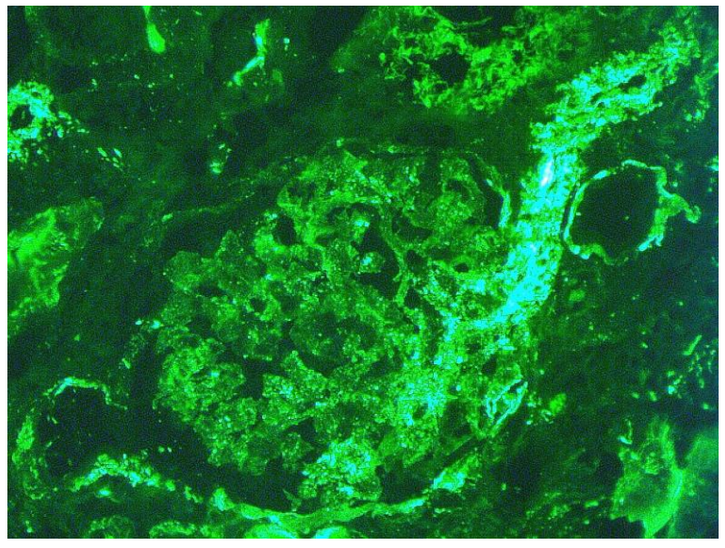
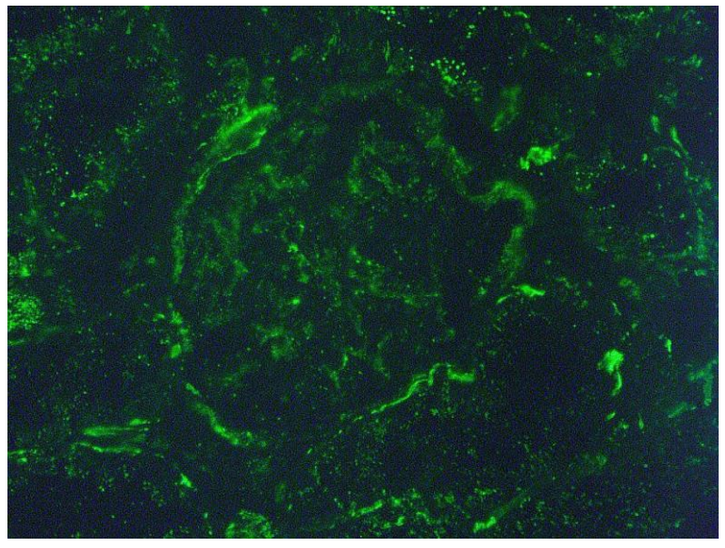
C5b9 expression on kidney biopsies

Three patients had a kidney biopsy:

Overexpression of C5b9 in the glomerular and tubular membrane and in capillary wall



Gemcitabine-induced TMA



Minimal change disease

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Is secondary TMA related to complement dysregulation?

Retrospective study, 1999-2017
aHUS French Registry HEGP VFB
n = 110 (Drugs 29%, Autoimmune disorders 24%, Inf° 17%, Malignancies 10%, Glomerulopathies 9%, Transplantation 8%, Pancreatitis 3%)

Low C3 = 9
Low C3 and C4 = 8
(9 lupus)

Rare Variants (< 0.1%)
n = 6 (3 FH, 1 FI, 2 THBD)
Pathogenic variants n = 2

No difference in healthy individuals

However, the homozygous MCP haplotype ggaac was more frequently found in patients with secondary HUS compared with control subjects (17% VS 6%)

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Le Clech et al. Kidney Int 2019

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Is secondary TMA related to complement dysregulation?

aHUS and secondary TMAs

Distinct presentations

No common genetic risk factors

Secondary TMA is an acute non relapsing form of HUS

Transient complement activation? (low C3 15%)

Systematic screening for complement gene variants not warranted in patients with secondary TMA

Interest of C5 blockade (n = 38) -> Same prognosis despite more severe patients

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Le Clech et al. Kidney Int 2019

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Kidney Diseases Associated With Anti-Vascular Endothelial Growth Factor (VEGF)

An 8-year Observational Study at a Single Center

DIAGNOSTIQUE	MAT, n=73	LGM/HSF, n=21
IVEGF	66 61 bevacizumab	1
TKI	3	20
DELAI (MOIS) MÉDIANE RANGE	 3 0,25 - 26	 2 0.25 - 30
CLINIQUE	HTA 83% - DFG N Pu 2.6 g/j Pu<1g: 31%	HTA 48% - DFG N Pu 3.15 g/j Pu<1g : 30%
SUIVI (MOY EN MOIS) SURVIE	15 53 %	13 26 %

Izzedine et al. Medicine 2014

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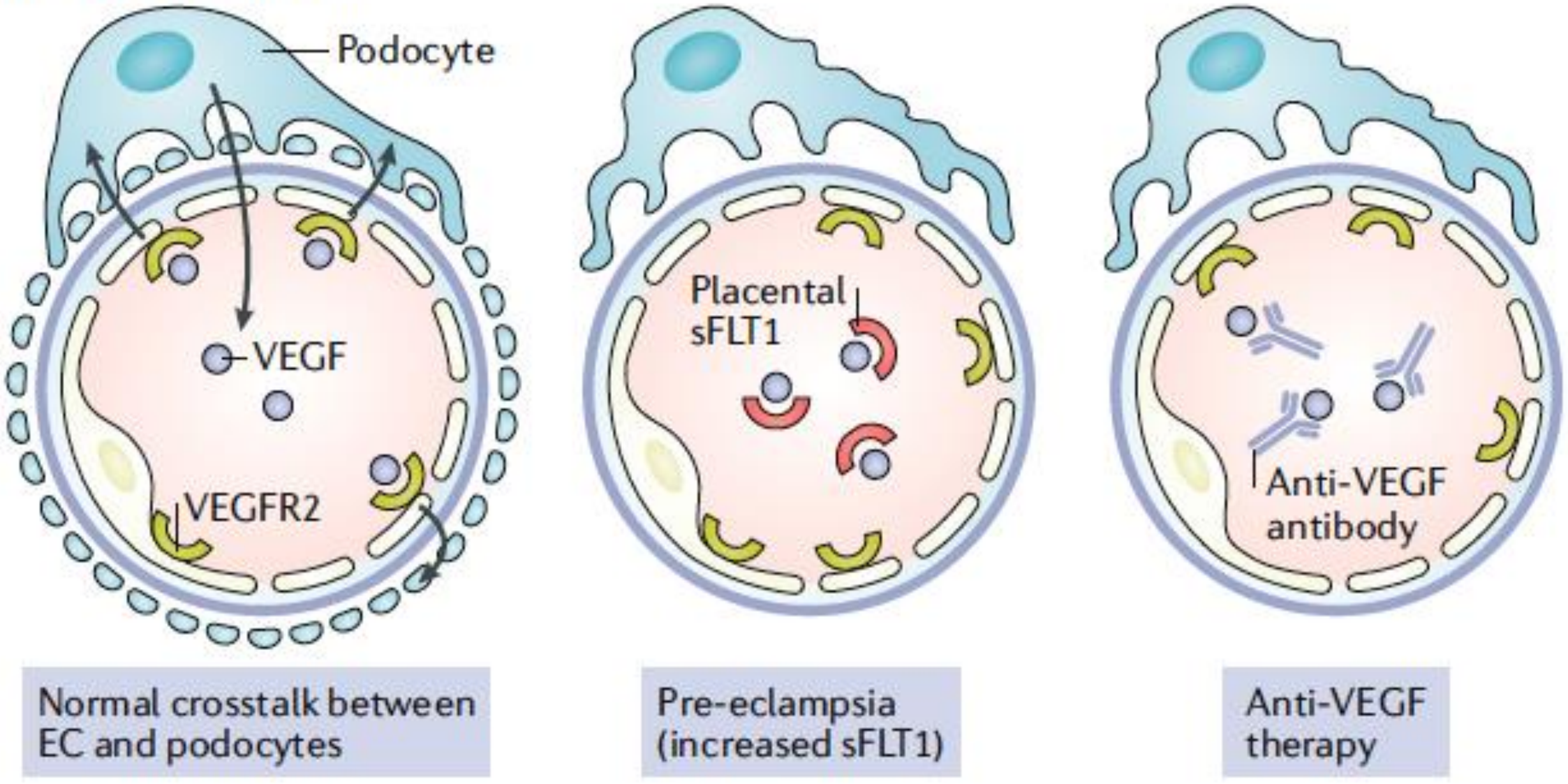
b VEGF inhibition



Normal crosstalk between EC and podocytes

Pre-eclampsia (increased sFLT1)

Anti-VEGF therapy

Jourde-Chiche et al. Nature Reviews Nephrology 2019

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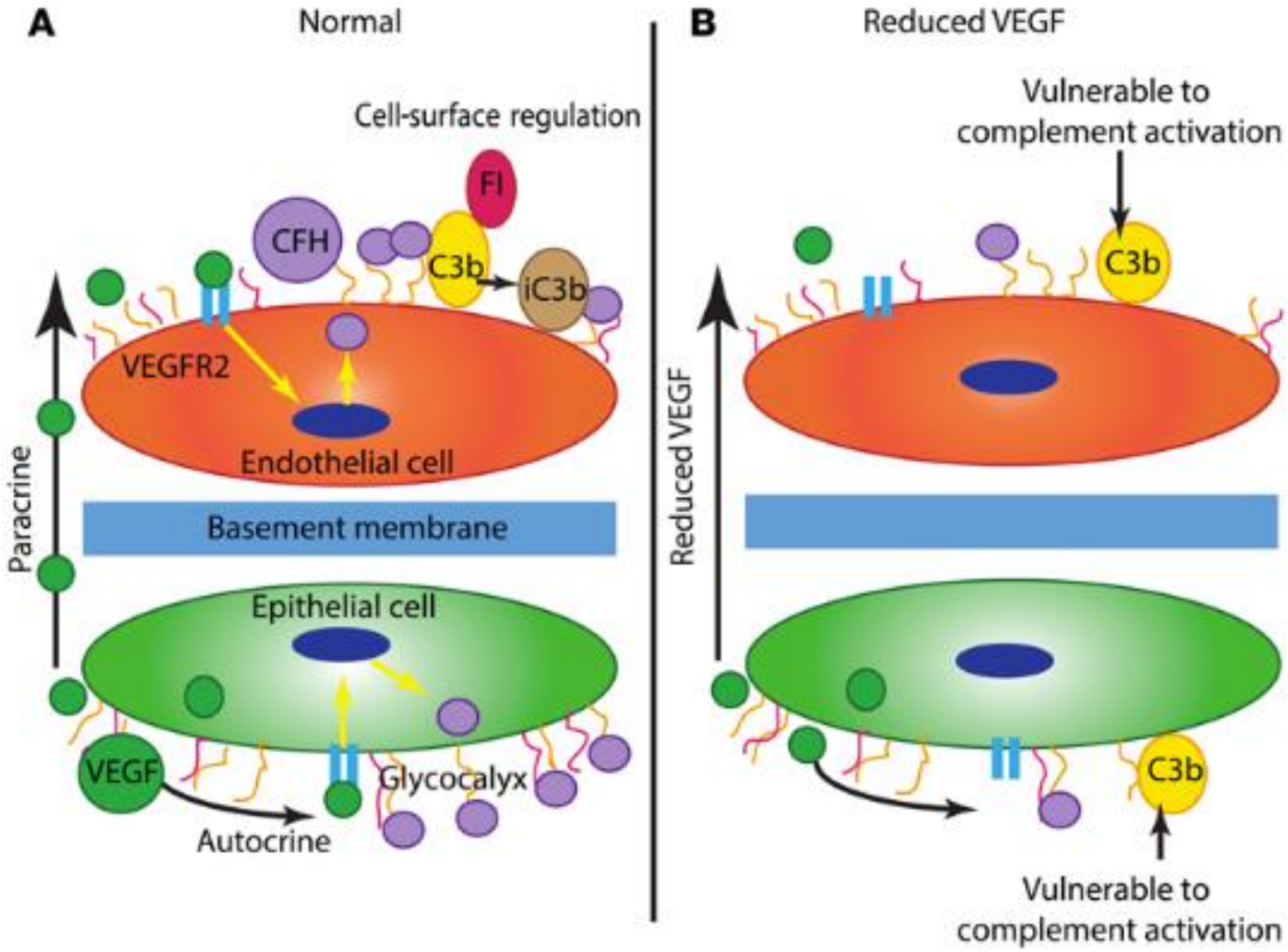
Anti VEGF et complément



VEGF is synthesized by podocytes

Paracrine effects on glomerular endothelial cells

-> Production of CFH by these cells

Anti-VEGF -> endothelial cells more vulnerable to complement activation

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Keir et al. J Clin Invest 2017

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Proteasome inhibitor associated TMA

TABLE I. Laboratory Values at TMA Diagnosis and Clinical Manifestations.

	Age and sex	PI used	Timing[a]	Hgb (g dL^{-1})	Platelet count, ×109/L	Cr (mg dL^{-1})	LDH (U L^{-1})	Hapto (mg dL^{-1})	ADAMTS13 activity	Dialysis required	TMA on renal biopsy	AST (U L^{-1})	GI sx	Neuro sx
1	70 M	Bortezomib	21 d	6.9	66	9.9	631	<14		Y		50	Y	N
2	64 M	Bortezomib	9 d	9.2	17	0.8	659	<14		N		118	N	N
3	51 M	Bortezomib	21 d	7.5	119	2.65	218	<2	34%	Y	Y	49	N	N
4	80 M	Carfilzomib	5 d	11.2	11	6.1	1920	<14	100%	Y		96	N	Y
5	79 M	Carfilzomib	8 mo	8.4	18	7.29	3481			Y		137	Y	Y
6	67 M	Carfilzomib	17 mo	10.3	20	3.12	642			N		43	N	N
7	64 F	Carfilzomib	8 mo	11.9	8	1.1	1848	<10	88%	N		123	Y	N
8	67 F	Carfilzomib	7 d	7.3	34	8.1	698	<8	79%	Y		36	Y	N
9	45 M	Carfilzomib	6 mo	4.6	163[b]	1.75	250	34		N		17	Y	Y
10	44 M	Carfilzomib	8 mo	6.7	39	7.28	1220	3		N	Y	58	Y	N
11	49 M	Carfilzomib	6 d	7.2	18	2.4	1129	<14	82%	N		36	N	N

- Normal ADAMTS 13 (n = 5, median = 82%)
- All patients had a normal C3, Genetic studies -> no mutations (CAP) revealed (n = 2)
- Half of the cases occurring within 14 days of drug initiation, and half occurring later in the treatment course (carfilzomib)
- NFκB inhibition -> VEGF pathway inhibition -> microvascular injury to the glomerular capillaries

bortezomib = Velcade
Carfilzomib = Kyprolis

Yui et al. AJH 2016

bjh short report

Complement as the enabler of carfilzomib-induced thrombotic microangiopathy

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Table I. Carfilzomib-induced thrombotic microangiopathy: patient characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4
Demographics and previous history				
Sex	Female	Female	Male	Male
Age, years	59	75	60	41
Diagnosis (year)	MM IgG kappa (2012)	MM BJ/lambda (2013)	MM IgA lambda (2010)	Relapsed solitary plasmacytoma (2017)
Number prior line treatments to CFZ	2	1	9	2
Previous autoSCT	Yes	Yes	Yes	Yes
CFZ-regimen administered	Kd (56 mg/m^2)	KRd (27 mg/m^2)	Kd (20 mg/m^2)	KRd (27 mg/m^2)
TMA associated with CFZ				
Date	September 2017	November 2017	August 2018	March 2019
CFZ cycle/day at presentation	Cycle 3, day 15	Cycle 1, day 15	Cycle 1, day 1	Cycle 6, day 2
TMA signs				
Haemoglobin, g/l [120–170 g/l]	68	69	70	64
Haematocrit, % [36–51%]	21	22	20	20
LDH, U/l [250–450 U/l]	3421	590	1645	2665
Haptoglobin, mg/dl [0·3–1·8 mg/dl]	Undetectable	Undetectable	Undetectable	Undetectable
Reticulocytes, $\times 10^9$/l [25–90 $\times$ 10^9/l]	157	121	94	230
Platelets, $\times 10^9$/l [150–400 $\times$ 10^9/l]	8	67	55	5
Creatinine, mg/dl [0·3–1·3 mg/dl]	6·25	2·77	4·77	13·67
Haemodialysis (number of sessions)	Yes (×4)	Yes (×3)	Yes (×3)	No

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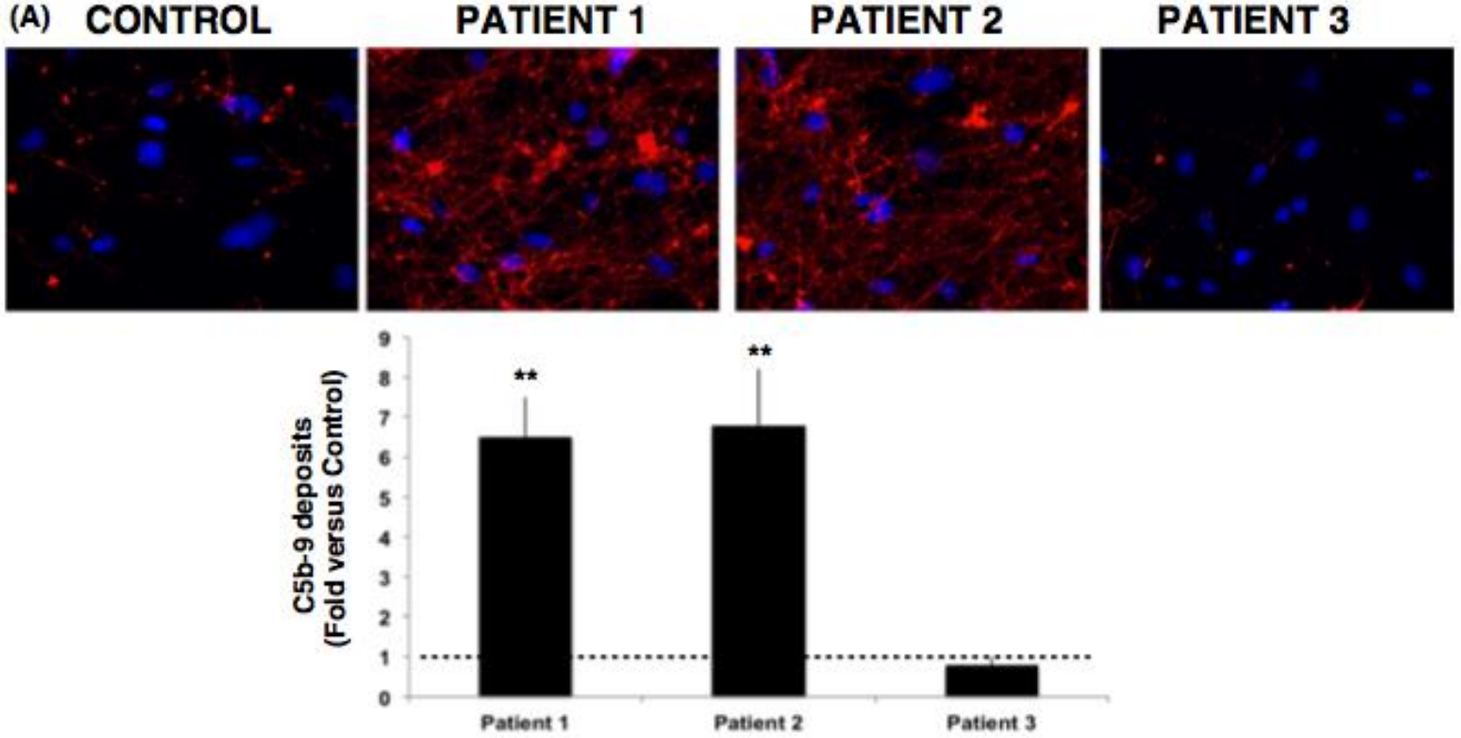
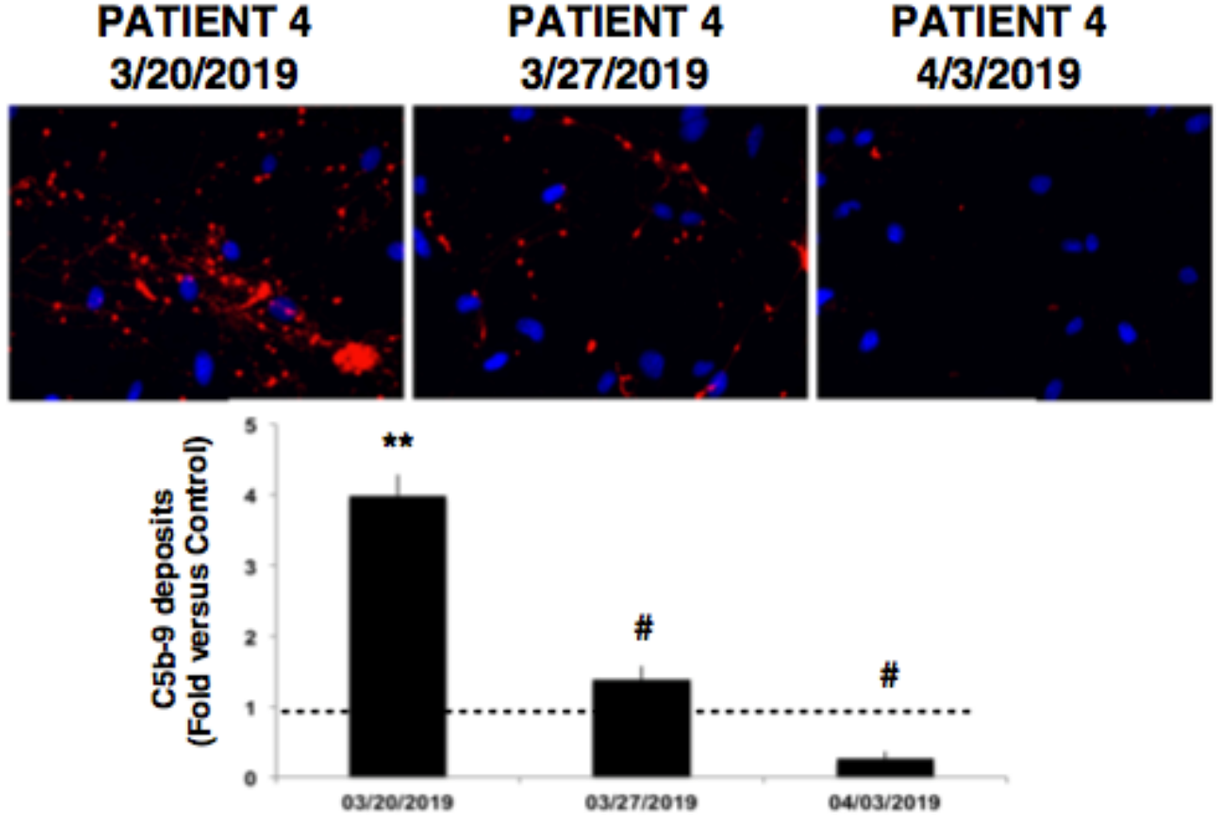
Blasco et al. BJH 2020

(A)



(B)



Membrane attack complex (C5b9) deposition on endothelial cells in culture exposed to plasma from patients during the acute phase of the disease suggests complement over activation in 3 out of 4 patients

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Treatment

- Screening +++ (HTA, Urine dipstick test)
- Treat hypertension (ACEIs, ARBs)…
- Specific treatment:

Possibility of spontaneous recovery 6-9 months

- Stop chemotherapy
- ~~Plasmapheresis~~
- ~~Steroids or other immunotherapies~~
- Complement C5 inhibition

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Conclusions

- FIRST, Cancer-associated TMA and chemo-associated TMA need to be distinguished on the basis of clinical evaluation

- Drug-induced TMAs -> several mechanisms -> endothelial toxicity, immune-mediated

- Normal ADAMTS 13 (except for ticlopidine), complement of alternative pathway disorders

- Importance of early diagnosis -> **Blood pressure monitoring, Proteinuria +++**

- No guidelines on the treatment which depends on the incriminated drug class -> Importance of obtaining an opinion from Regional Reference Centers

- The data presented today is biased !

- Publication bias (success), simple cases unreported

- New French Registry for drug-induced TMAs (underestimated)

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