Drug-induced Thrombotic Microangiopathies

Actualités Néphrologiques Jean Hamburger 11 Mai 2022

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Conflicts of interests

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

Travel support: Alexion, Octapharma, Sanofi

cnr-mat

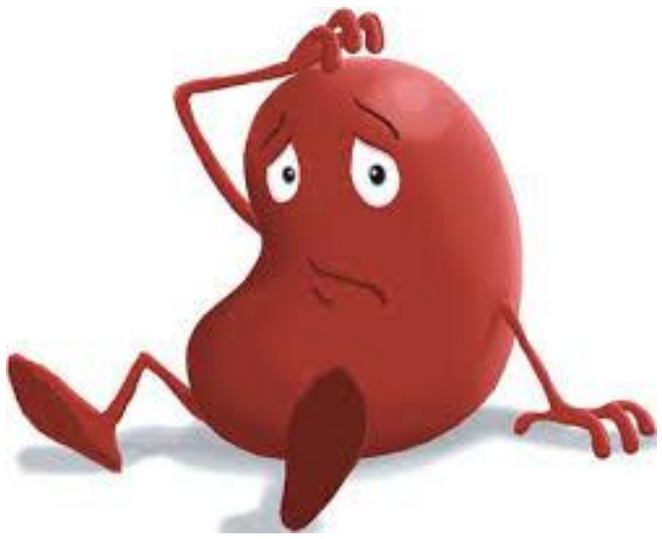
European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

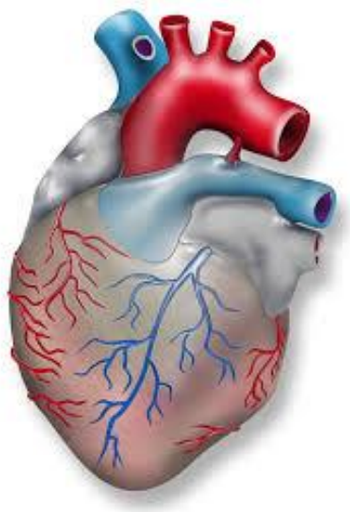
What is TMA?

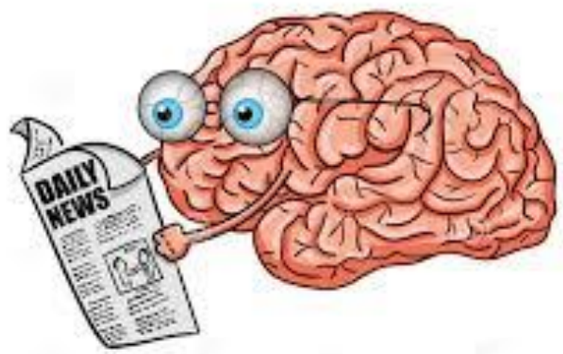
Microangiopathic hemolytic anemia

Peripheral thrombocytopenia

Organ failure of variable severity







Primary TMA: hereditary

Primary TMA: acquired

aHUS with complement gene mutation

TTP with *ADAMTS13* mutation

DGKE TMA

cblC deficiency mediated TMA

aHUS with FH autoantibody

TTP with ADAMTS13 autoantibody

De novo TMA after solid organ transplant

Pregnancy associated TMA

HELLP

Unexplained TMA

STEC-HUS

AAV

IgAN

MN

TMA with glomerular diseases

FSGS

C3G/MPGN

TMA after bone marrow transplant

TMA with severe hypertension

Drug induced TMA

TMA with autoimmune conditions

CAPS

SRC

SLE

Malignancy associated TMA

Pneumococcal HUS

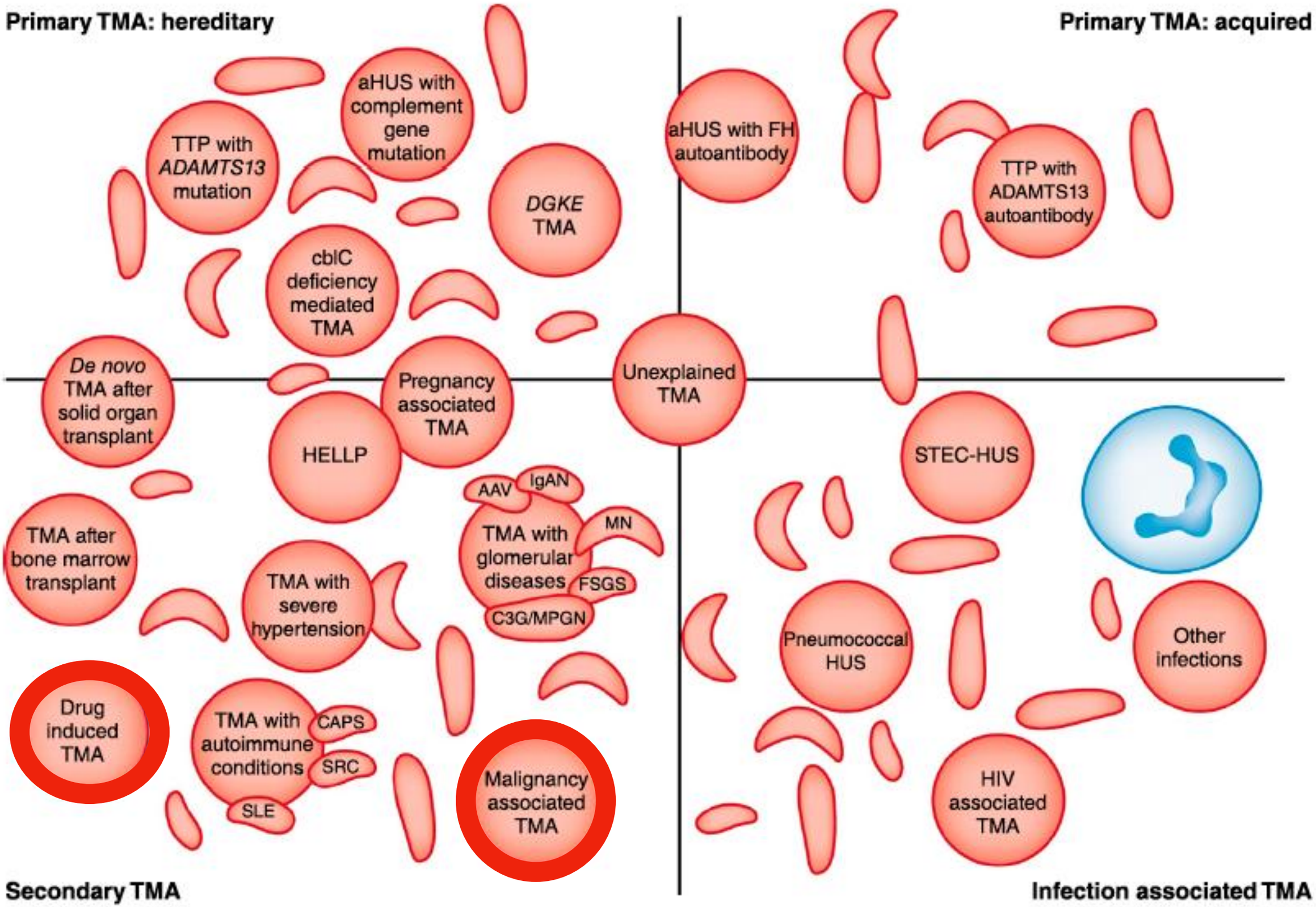
Other infections

HIV associated TMA

Secondary TMA

Infection associated TMA

Brocklebank. CJASN 2018



Brocklebank. CJASN 2018

Etiologies et pronostic des microangiopathies thrombotiques

Rretrospective study: 564 consecutive patients between 2009 and 2016 (CHU Tours)

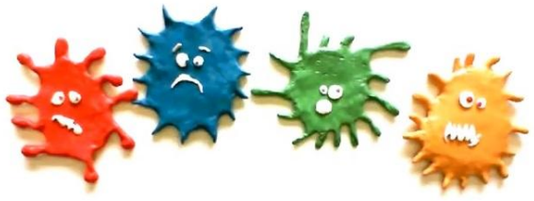
Primary TMAs 6%

TTP 3%

aHUS 3%

Secondary TMAs 94%

35%



33%

26%

19%

UNDERDECLARED

Bayer et al. CJASN 2019

Etiologies et pronostic des microangiopathies thrombotiques

Rretrospective study: 564 consecutive patients between 2009 and 2016 (CHU Tours)

Primary TMAs 6%

TTP 3%

aHUS 3%

Secondary TMAs 94%

35%

CNIs 68%
gemcitabine 8%
Anti-VEGF 3%

26%

33%

19%

UNDERDECLARED

Bayer et al. CJASN 2019

Epidemiology: burden of patients

Proportion of chemo-associated TTP (from 772 TTP patients)

	Number of patients (proportion of 772 TTP)
Infections	94 (12%)
AI diseases	87 (11.5%)
Cancer	71 (9%)
Pregnancy	62 (8%)
Transplantation	27 (3.5%)
HIV	24 (3%)
Other / several conditions	18 (2,5%)
Drugs	11 (1.5%)

> 100 chemo-associated TMA in the French TMA registry

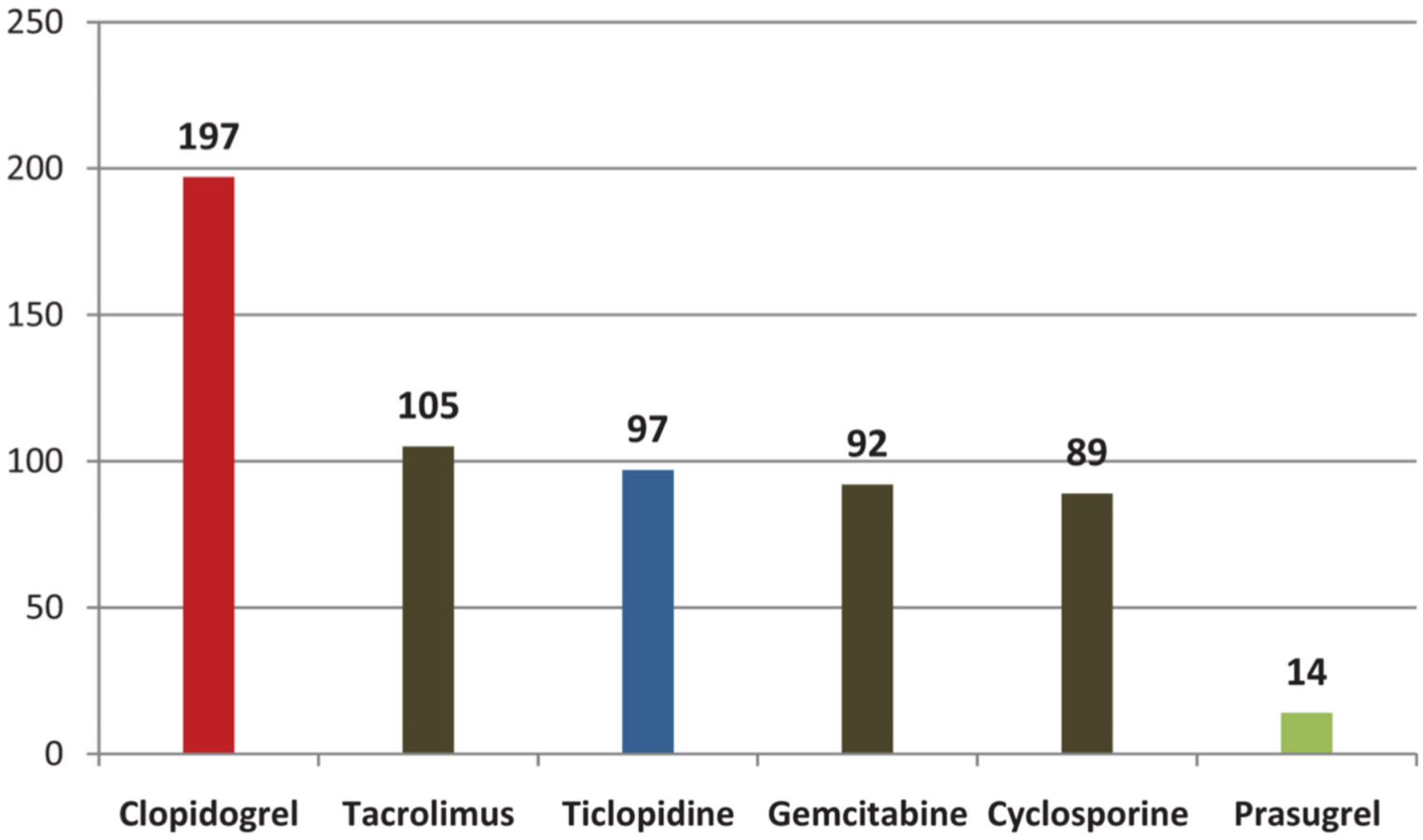
> 90% of patients have a detectable activity

Underdeclared+++++

Most chemo-associated TMA have a detectable ADAMTS13 activity (= not TTP)

Mariotte et al., Lancet Haematol 2016 and unpublished results

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

Jacob et al. Semin Thromb Hemost 2012

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

Reese et al. AJH 2015

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

Update
2014-2018

TABLE 1 Drug-induced thrombotic microangiopathy (TMA), 2014-2018: 8 drugs with definite evidence supporting a causal association with TMA that had not been previously reported with definite evidence

Drug	Patients (no.)	Comments
Opioids		
Oxymorphone (Opana ER)	28	9 reports, 28 patients. 1 report[3] described 18 episodes of Opana ER-induced TMA in 15 patients in one hospital for 14 months. 1 report[4] documented that polyethylene oxide (PEO), an inert ingredient added to Opana ER tablets to deter IV abuse, was the etiology, not the opioid.
Oxycontin	3	3 reports. Oxycodone reformulated with the addition of PEO was introduced in Australia in 2014. These 3 reports were published in 2015–2017, each describing 1 patient. The presumed etiology of TMA was PEO, the same as with Opana-ER.
Proteasome inhibitors		
Bortezomib	1	In this report,[5] only patient 3 had sufficient data for evaluation; he had recurrent TMA when bortezomib was resumed 18 months after his initial episode. 2 additional patients with TMA attributed to bortezomib were only presented in a table.
Carfilzomib	4	3 reports. In the Yui et al.'s report,[5] only patient 11 had sufficient data for evaluation; he had recurrent TMA twice with 2 recurrent doses of carfilzomib. Seven additional patients with TMA attributed to carfilzomib were only presented in a table.
Ixazomib	1	This patient only received one dose of ixazomib. The authors suggested that the adverse reaction manifested as TMA may be a class effect of proteasome inhibitors.
Cyclin-dependent kinase (CDK4, CDK6) inhibitor		
Palbociclib	1	TMA occurred after 2 weeks of daily palbociclib. The patient also received fulvestrant, which had been given continuously for the previous 3 years.
Blood product		
Intravenous immunoglobulin (IVIg)	2	1 report. Both patients had kidney allograft failure and BK viremia. IVIg was given to treat BK infection and facilitate immunosuppressive dose reduction. Symptoms promptly followed infusion. Authors speculated that TMA may be related to the brand of IVIg.
Anticonvulsive agent		
Valproic acid	1	Valproate commonly causes thrombocytopenia by dose-dependent marrow suppression. In this patient, TMA occurred during valproic acid intravenous infusion when serum levels (130-137 μg/mL) exceeded the therapeutic range (50-100 μg/mL).

Rabia Saleem, James N George et al. AJH 2018

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

Grangé, Coppo . Néphrologie et Thérapeutique 2017

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

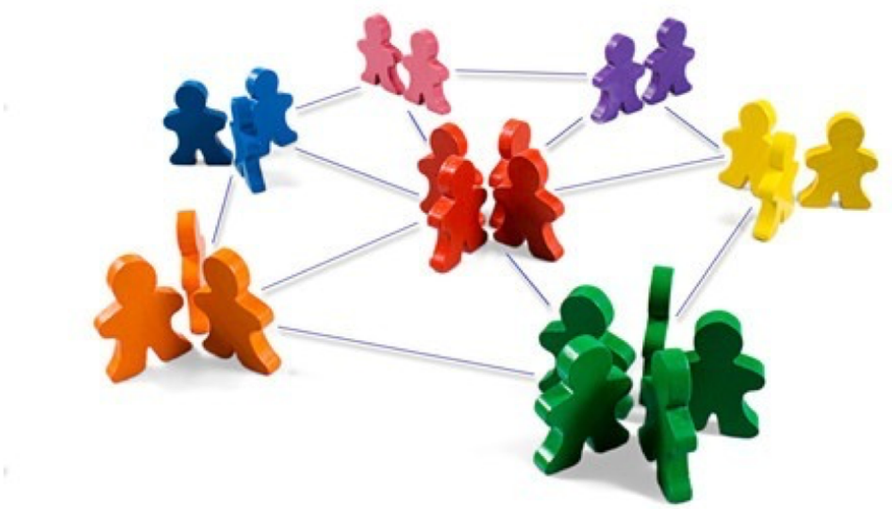
Poor response to plasma exchange ± immunoadsorption

Poor prognosis; death at ~ 4 months

Paul Coppo's slide

Appel à observations
MAT et Mitomycine
+/- eculizumab

Clément Maho (interne DES néphrologie Strasbourg)
Pr Bruno Moulin



Rouen, Lille, Amiens, Toulouse, Strasbourg

Merci à tous les acteurs de ce projet

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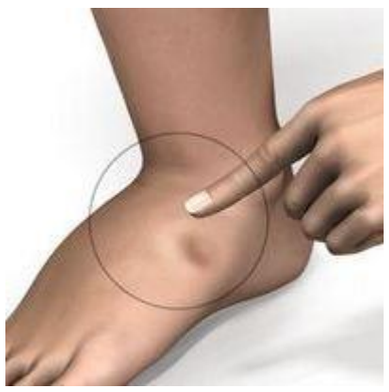
GEMCITABINE-induced TMAs

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%

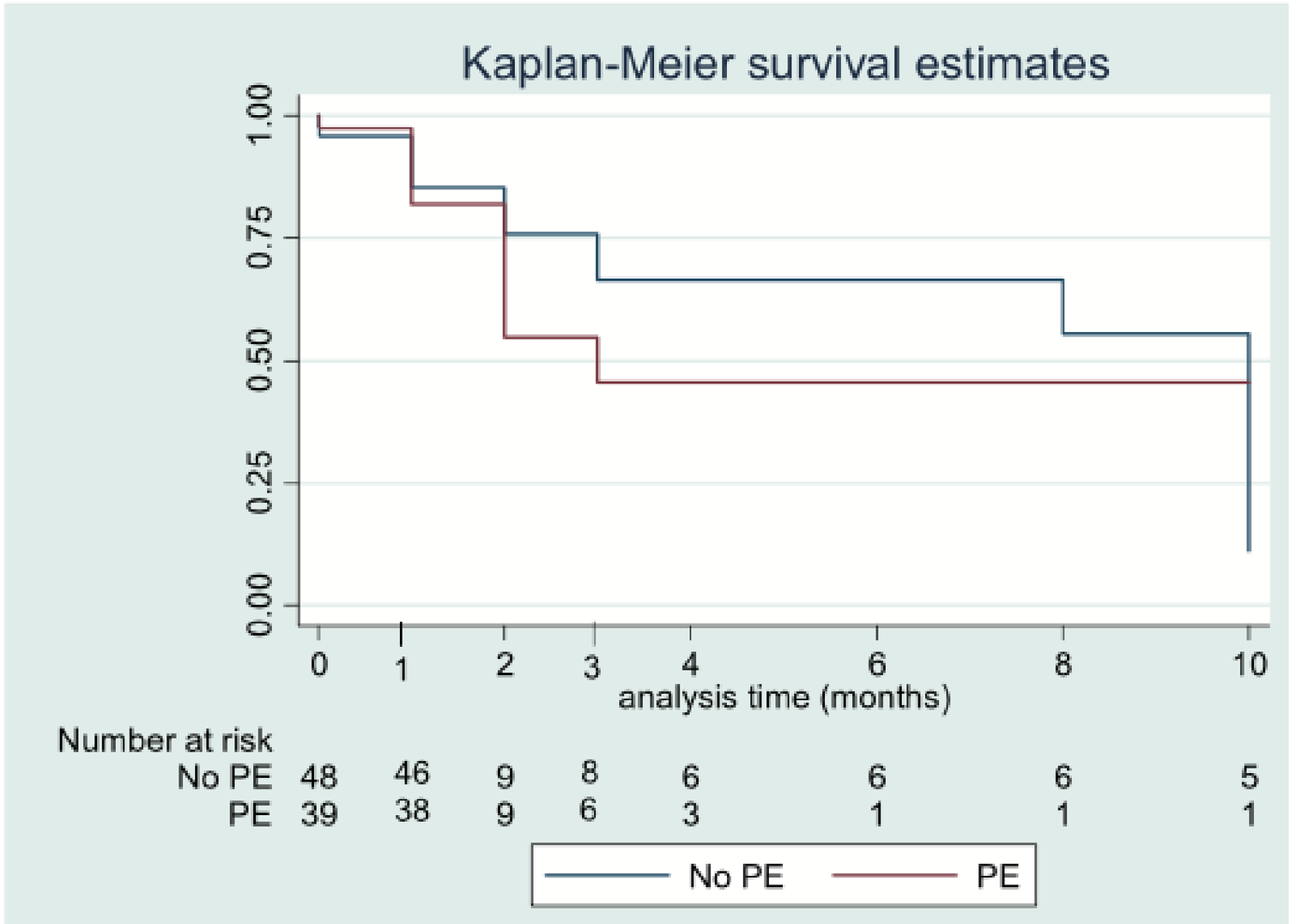
Daviet et al. British Journal of Clinical Pharmacology 2019

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%

Daviet et al. British Journal of Clinical Pharmacology 2019

GEMCITABINE-induced TMAs



Renal characteristics

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

Daviet et al. British Journal of Clinical Pharmacology 2019

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*]

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

Grall, Grangé et al. BMC Nephrology 2021

Methods

Definitions of outcome:

Hematological remission :
normalization of hematological value (platelet count and LDH level)

Renal remission :

- ➢ **Complete** if serum creatinine level returned to baseline
- ➢ **Partial** if serum creatinine level decreased by 15%

Grall, Grangé et al. BMC Nephrology 2021

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)

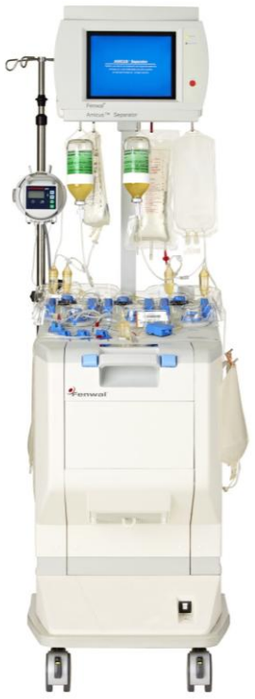
Cumulative dose: 27.5 g (range, 9.0-48)

Grall, Grangé et al. BMC Nephrology 2021

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)



Grall, Grangé et al. BMC Nephrology 2021

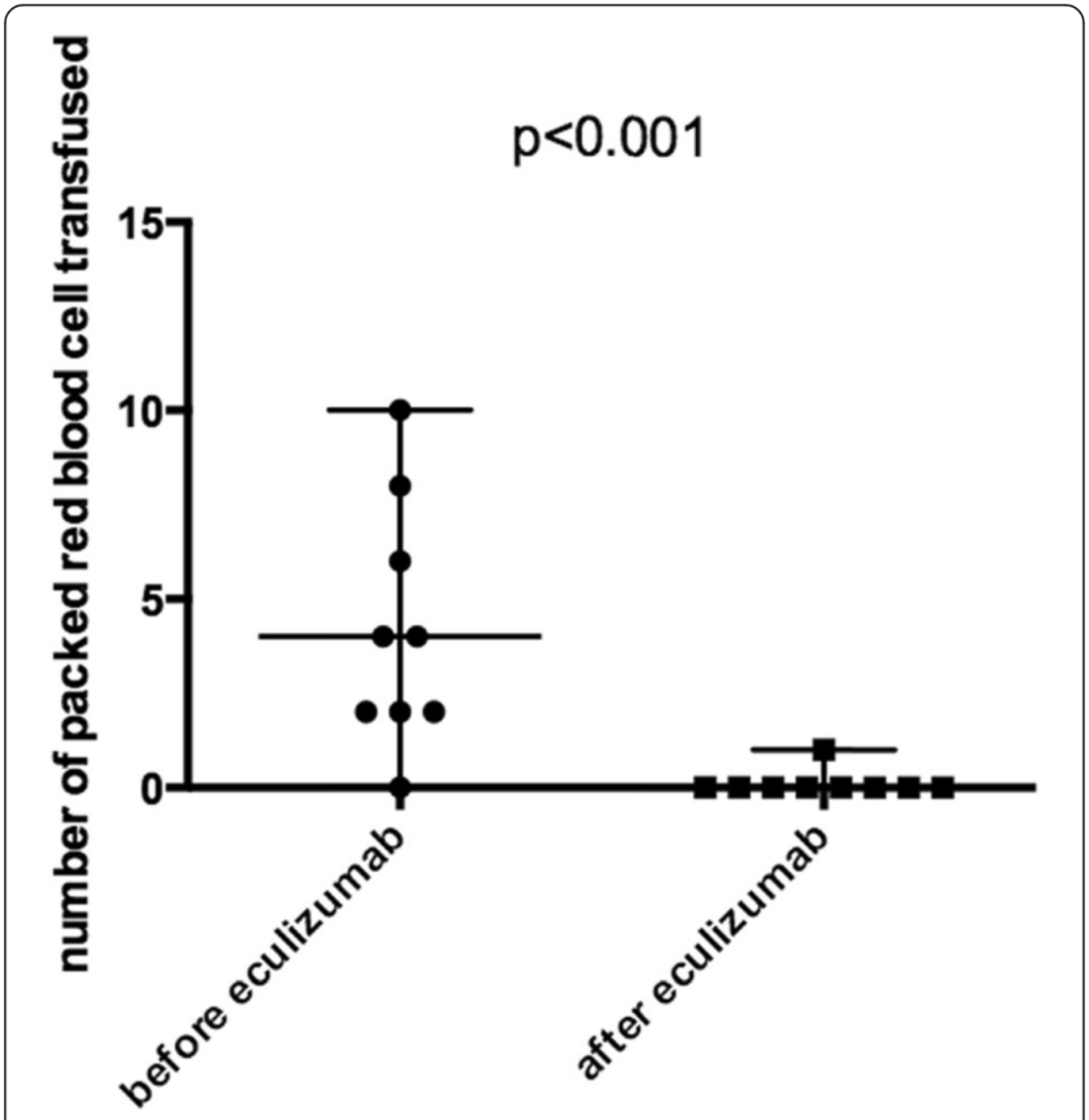


Fig. 2 Comparison of packed red blood cell transfusion before and after eculizumab therapy. Quantitative values are expressed as median with range

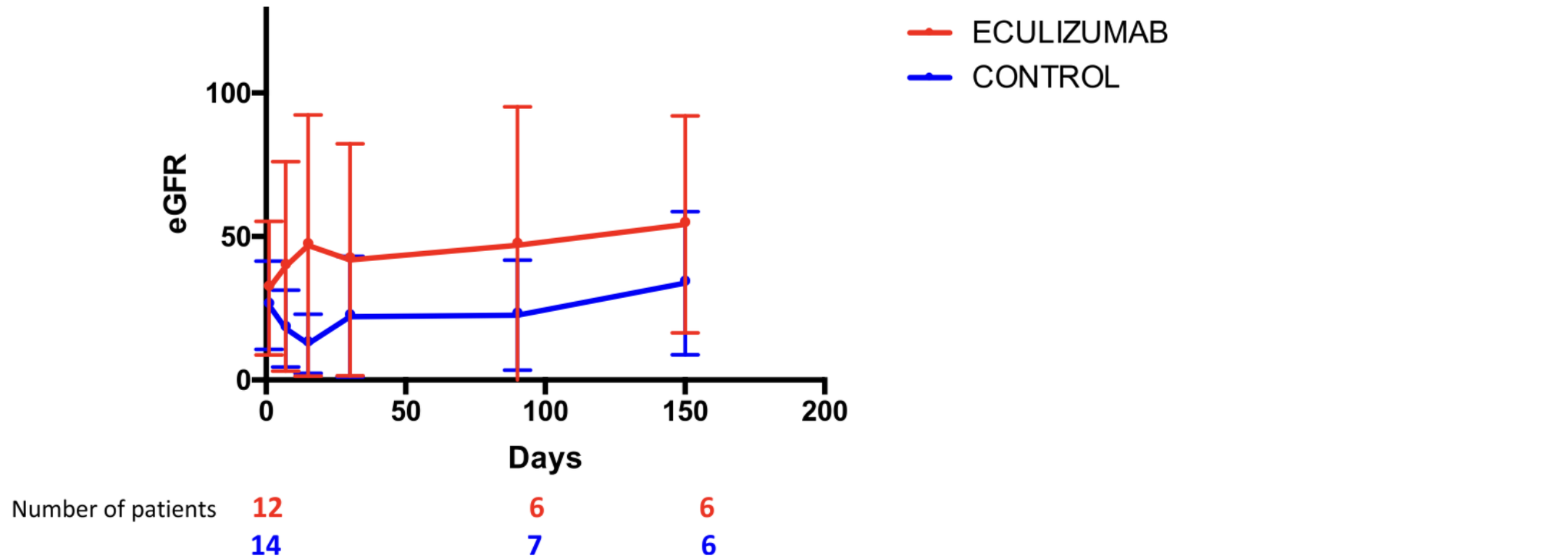


Fig. 3 Evolution of renal function as a function of time in the eculizumab group and in the control group. Values expressed as mean and standard deviations

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)

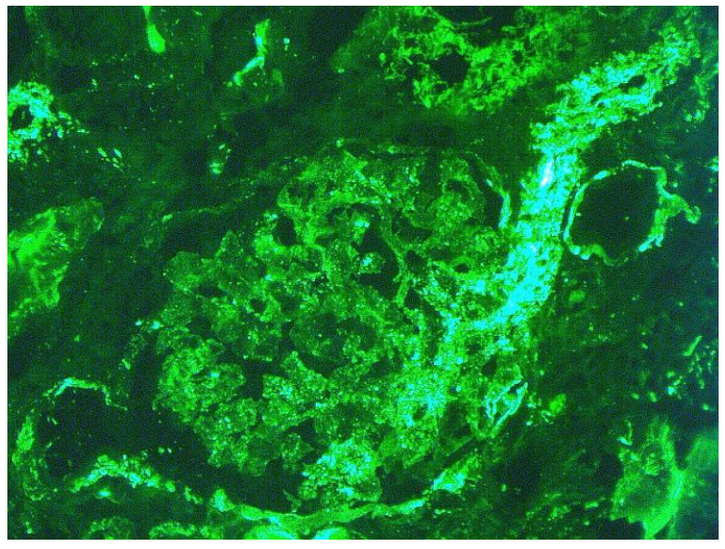
eGFR Estimated glomerular filtration rate. Quantitative values are expressed as median with range

Grall, Grangé et al. BMC Nephrology 2021

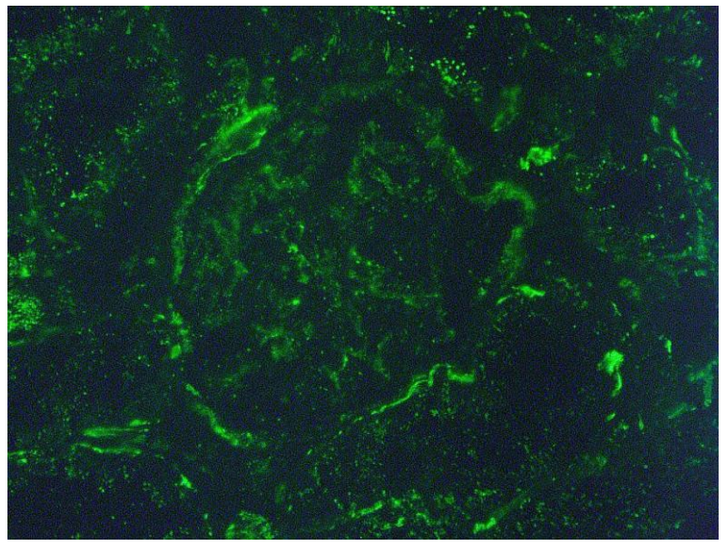
C5b9 expression on kidney biopsies

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

Grall, Grangé et al. BMC Nephrology 2021

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%)

Le Clech et al. Kidney Int 2019

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 in patients with secondary TMA

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

Le Clech et al. Kidney Int 2019

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

anti-VEGF-induced TMAs

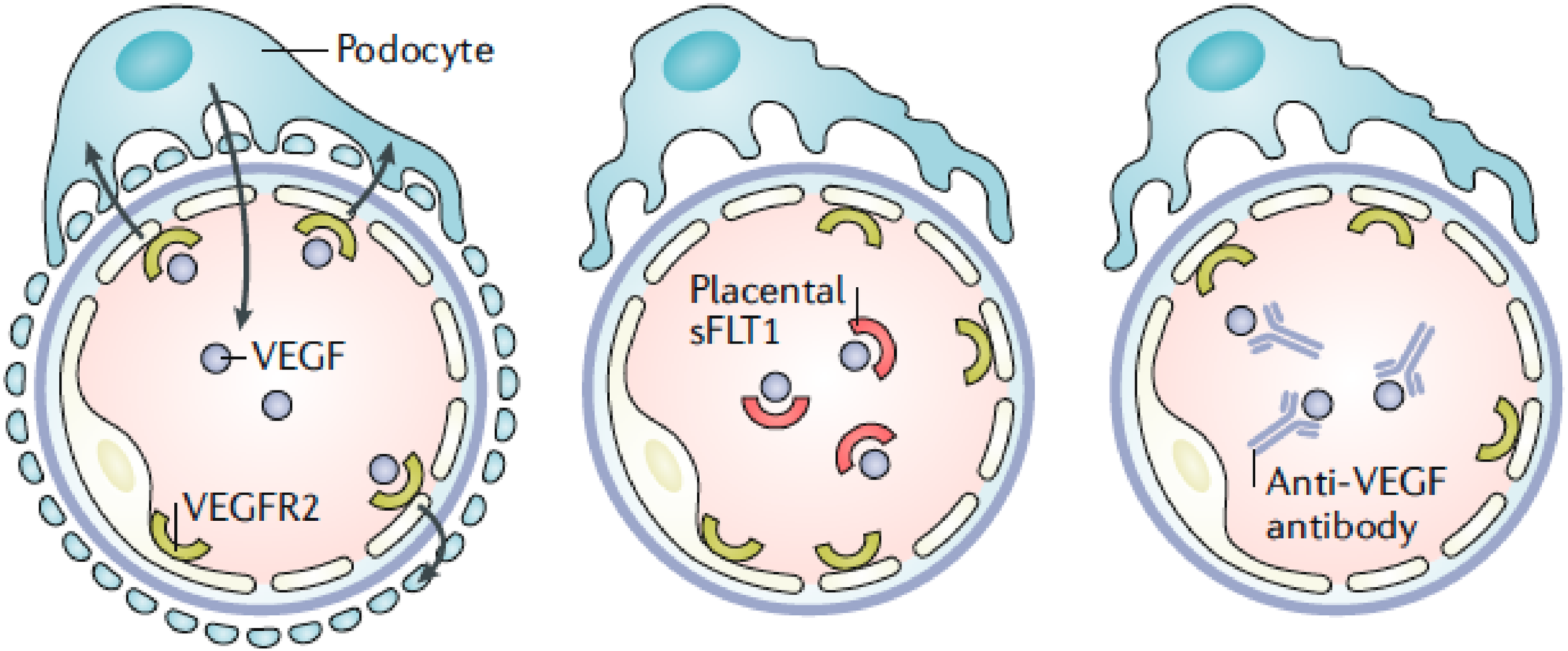
Eremina: 6 patients treated with bevacizumab, reversibility of TMA after cessation of treatment
Mice: Conditional gene targeting to delete VEGF from renal podocytes -> profound thrombotic glomerular injury

Hypothesis: Authors posit that a loss of VEGF from the glomerulus leads to a loss of the healthy fenestrated phenotype and promotes the development of microvascular injury and thrombotic microangiopathy.

- **Improvement after cessation of treatment +++,** need for multidisciplinary consultation to know if treatment can be continued (or not)

Eremina et al. NEJM 2008
Izzedine et al. Kidney International 2013

b VEGF inhibition



Normal crosstalk between EC and podocytes

Pre-eclampsia (increased sFLT1)

Anti-VEGF therapy

Jourde-Chiche et al. Nature Reviews Nephrology 2019

Nephrol Dial Transplant (2014) 29: 325–332
doi: 10.1093/ndt/gft465
Advance Access publication 2 December 2013

ndt
Nephrology Dialysis Transplantation

Original Articles

All anti-vascular endothelial growth factor drugs can induce 'pre-eclampsia-like syndrome': a RARe study*

RARe Registry: **R**eins sous ttt **A**nti VEGF **Re**gistre

22 patients with malignancies treated by antiVEGF ->
renal biopsies 16 +/- 10 months after beginning of treatment
for renal carcinoma without proteinuria
21 Hypertension
Mean proteinuria = 2.97 g/24h
Mean serum creatinine = 134 µmol/l

Vigneau et al. NDT 2014

Table 4. Expression of podocin, nephrin, synaptopodin, and VEGF (by immunochemistry), number of glomeruli per section and percentage of acute tubular necrosis in renal biopsies from the 22 patients with proteinuria and/or renal failure during adjuvant anti-angiogenic treatment

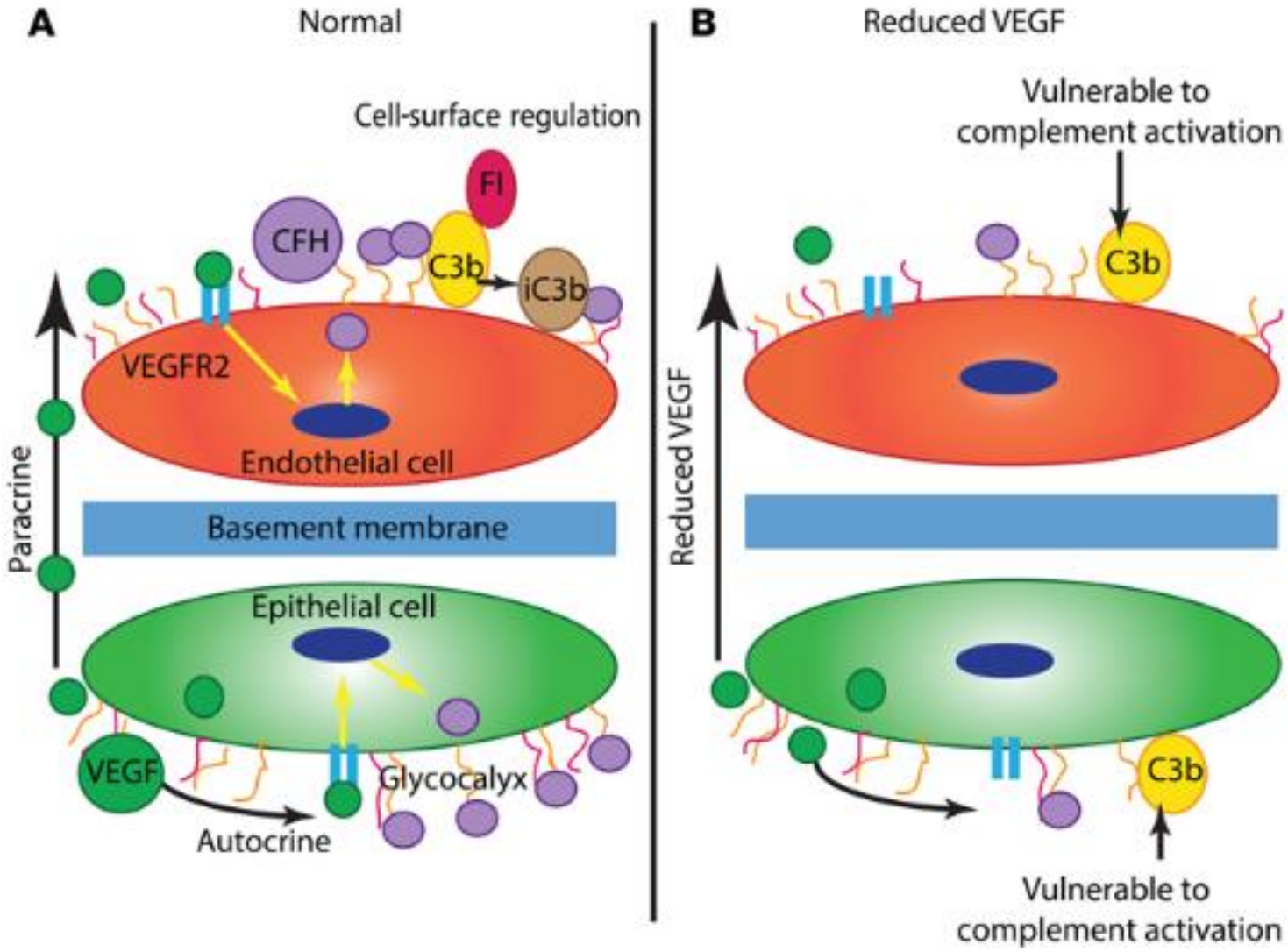
No. of patient	Number of glomeruli	Podocin	Nephrin	Synaptopodin	VEGF	ATN (%)
1	14	0/+	0	+	0/+	0
2	27	0	++	++	1	0
3	5	0	0	0 /+	NA	>50
4	20	0	0	NA	?NA	0
5	10	0	+	0	NA	0
6	5	+	+	0	+	15
7	10	+	0 /+	+	NA	30
8	7	0	+	+/++	ND	0
9	7	0	+	+	0/+	0
10	13	0	++	0 /+	0/+	20
11	5	0	0	0 /+	0/+	10
12	13	0	0	0	0	30
13	11	0	0	0 /+	0/+	<10
14	13	0	++	++	0	0
15	27	0	++	++	0/+	0
16	10	0	+	+	0/+	40
17	14	0	0 /+	+	0 /+	0
18	22	0	0	0	0 /+	<10
19	12	0	0	+	0	0
20	10	0	0	0	0 /+	<20
21	10	0	0 /+	+	0 /+	0
22	16	0	0 /+	0	0 /+	<10

Score: 0, no expression; 1, mild expression and 2, strong expression. The number of analysed glomerular cross-sections is reported on the second column. The percentage of ATN in renal biopsy sections is reported in the right column.
NA, not available.

Nephrin, podocin and synaptopodin were variably down-regulated in all renal biopsies. VEGF was down-regulated in all glomeruli.

Vigneau et al. NDT 2014

Anti VEGF et complément



VEGF synthesized podocytes

Paracrine effects on glomerular endothelial cells

-> Production of CFH by these cells

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

Keir et al. J Clin Invest 2017

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

EXCEPTIONAL CASE REPORT

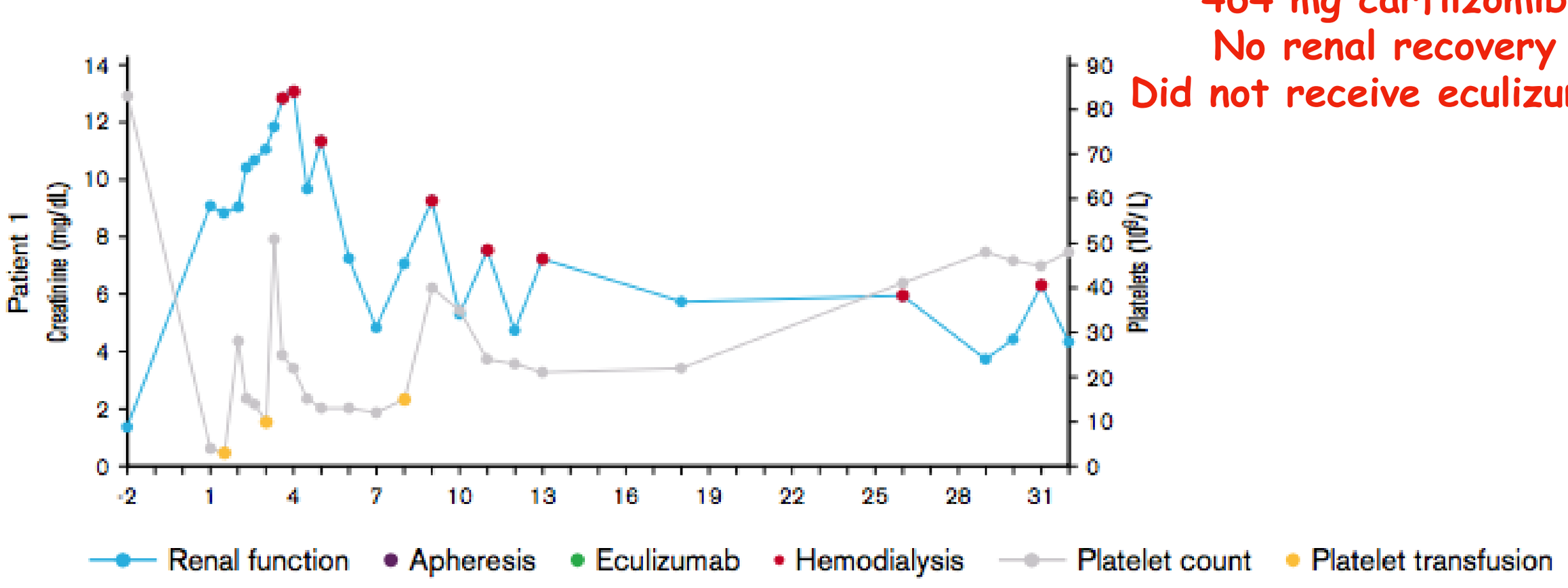
blood advances

Carfilzomib-induced aHUS responds to early eculizumab and may be associated with heterozygous *CFHR3-CFHR1* deletion

Andrew Jay Portuguese[1] and Brea Lipe[2]

[1]Department of Internal Medicine and [2]Department of Hematology/Oncology, University of Rochester, Rochester, NY

Patient 1
Plasma cell leukemia
Autologous
stem cell transplant
Carfilzomib/Lenalidomide
464 mg carfilzomib
No renal recovery
Did not receive eculizumab



Portuguese et al. Blood Advances 2018

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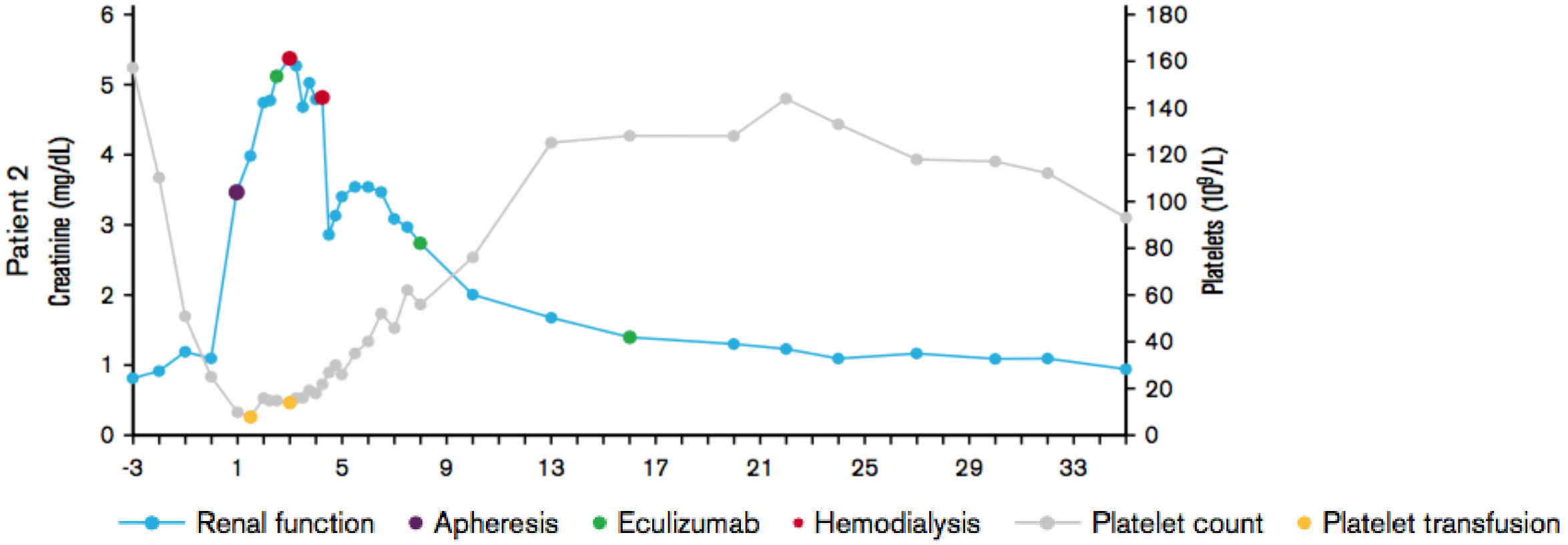
Patient 2
Multiple myeloma
Autologous
stem cell transplant
carfilzomib/lenalidomide
1826 mg carfilzomib



Portuguese et al. Blood Advances 2018

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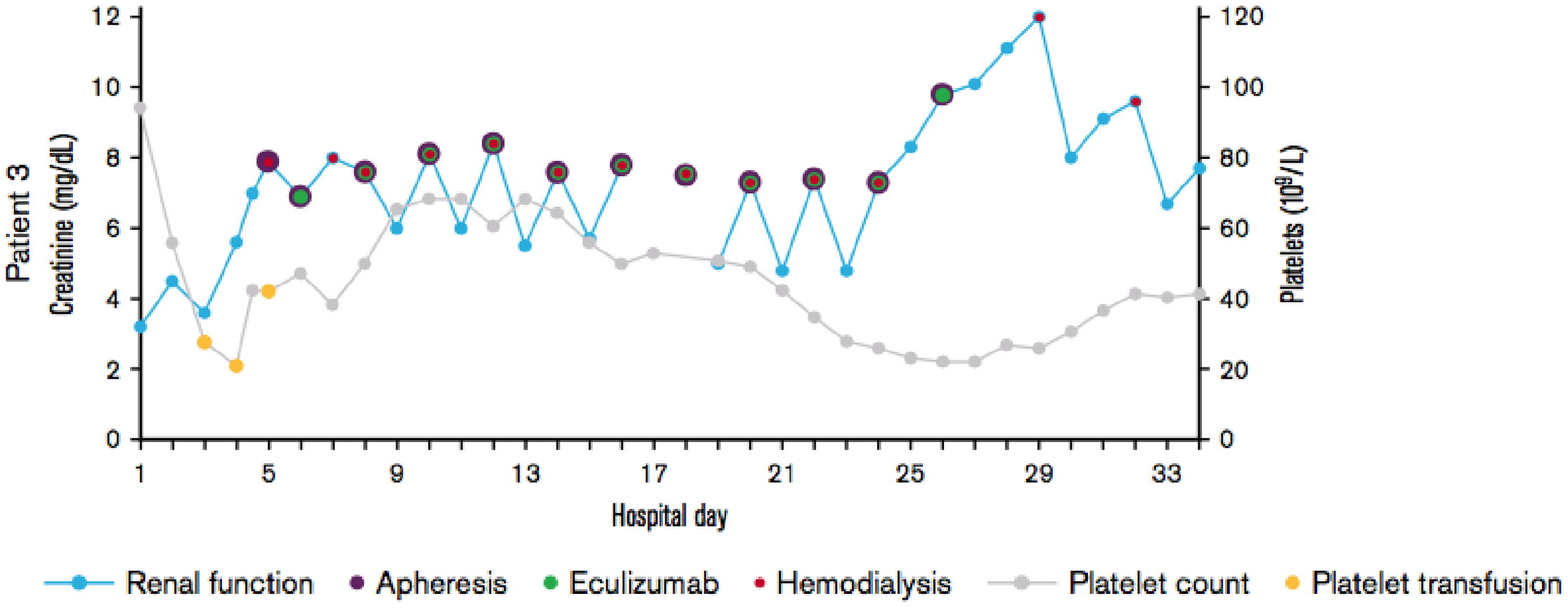
[1]Department of Internal Medicine and [2]Department of Hematology/Oncology, University of Rochester, Rochester, NY

Patient 3
Plasma cell leukemia
cyclophosphamide/carfilzomib
329 mg carfilzomib



Portuguese et al. Blood Advances 2018

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Patients 1 and 2: were found to harbor heterozygous CFHR3-CFHR1 deletions
Functional alternative complement pathway testing: Unremarkable in all 3 patients

A common homozygous deletion encompassing CFHR3 and CFHR1 genes is associated with aHUS
Heterozygous deletion is considered a common benign variant

BUT
Proteasome inhibition in vitro -> decreases CFH expression
-> uncontrolled complement activation on cell and tissue surfaces ->
Increases cytotoxic effect of complement activation

Portuguese et al. Blood Advances 2018

bjh short report

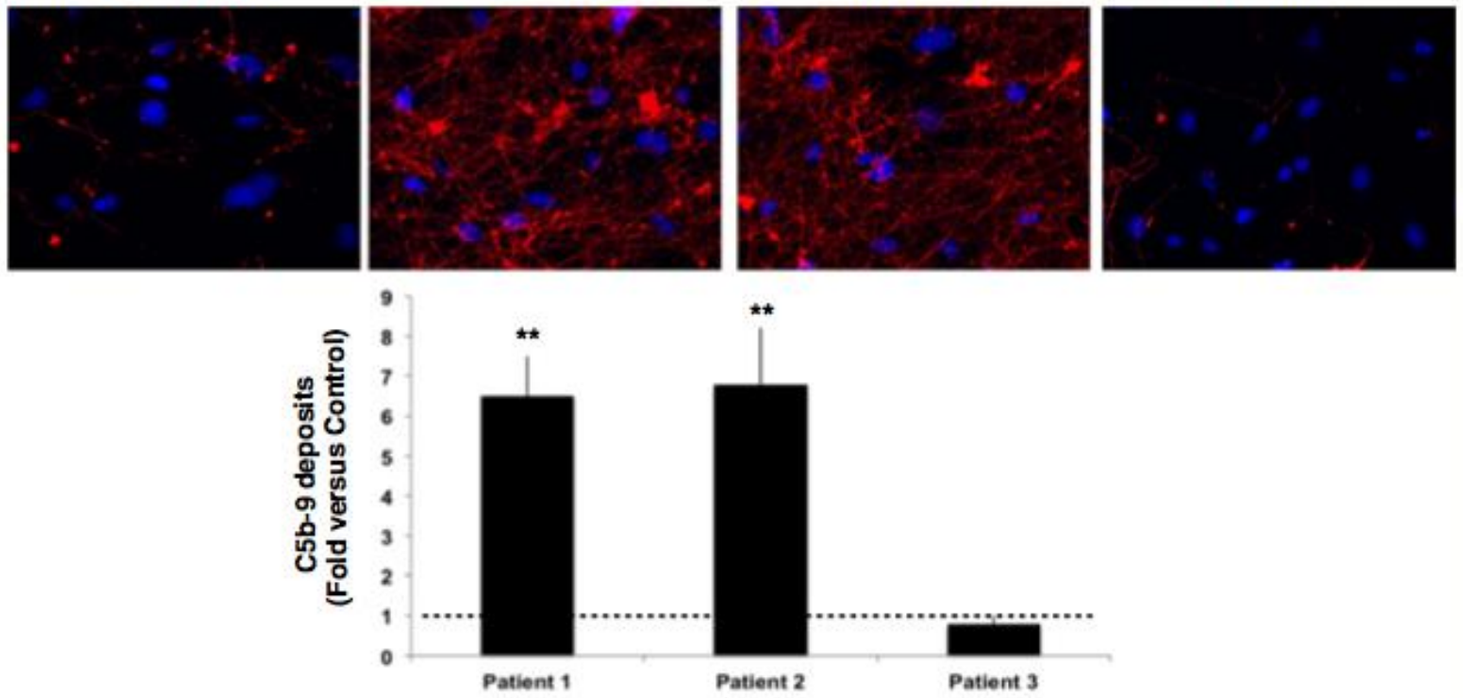
Complement as the enabler of carfilzomib-induced thrombotic microangiopathy

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

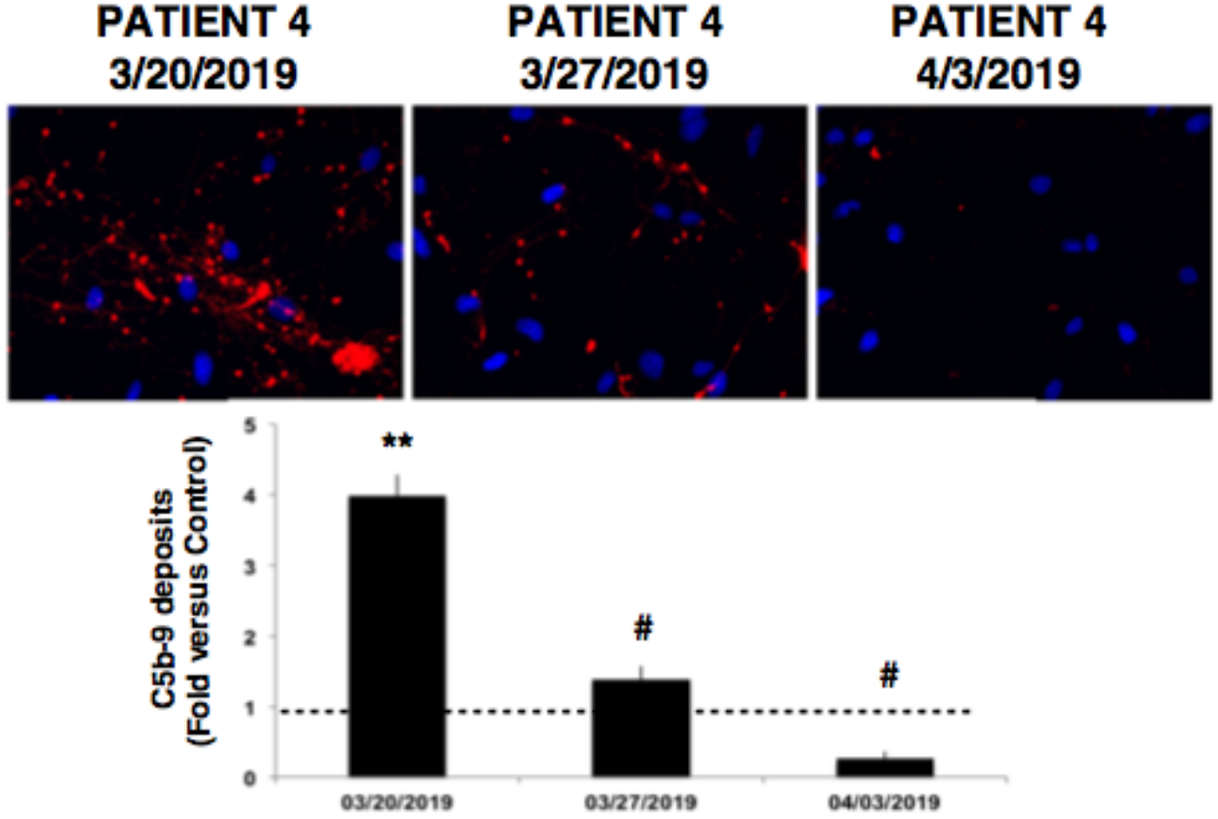
	Patient 1	Patient 2	Patient 3	Patient 4
Demographics and previous history				
Sex	Female	Female	Male	Male
Age, years	59	75	60	41
Diagnosis (year)	MM IgG kappa (2012)	MM BJ/lambda (2013)	MM IgA lambda (2010)	Relapsed solitary plasmacytoma (2017)
Number prior line treatments to CFZ	2	1	9	2
Previous autoSCT	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

Blasco et al. BJH 2020

(A) CONTROL PATIENT 1 PATIENT 2 PATIENT 3



(B) PATIENT 4 3/20/2019 PATIENT 4 3/27/2019 PATIENT 4 4/3/2019



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

Blasco et al. BJH 2020

Treatment

- Screening +++ (HTA, Urine dipstick test)
- Treat hypertension (ACEIs, ARBs)…
- Specific treatment:
  - Stop chemotherapy
  - ~~Plasmapheresis~~
  - ~~Steroids or other immunotherapies~~
  - Complement C5 inhibition

Possibility of spontaneous recovery 6-9 months

CASE REPORT Open Access

Ipilimumab-induced thrombotic thrombocytopenic purpura (TTP)

Jeanelle King[1], Javier de la Cruz[2] and Jose Lutzky[1*]

68 yo woman
Stage 3 melanoma pT2N2M0

Ipilimumab 10 mg/kg/3 weeks
TTP 19 days after 3rd cycle

Hb 6.8 g/dl, Platelets 7 giga/L, LDH > 7000 UI/L
Presence of schistocytes
Creatinine 246 micromol/L
ADAMTS13 activity < 3%, Anti ADAMTS13 Ab +

Good outcome after ttt with steroids/antiCD20/ plasmapheresis
Discontinuation of ipilimumab

King et al.
Journal for Immunotherapy of Cancer 2017

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 +++**

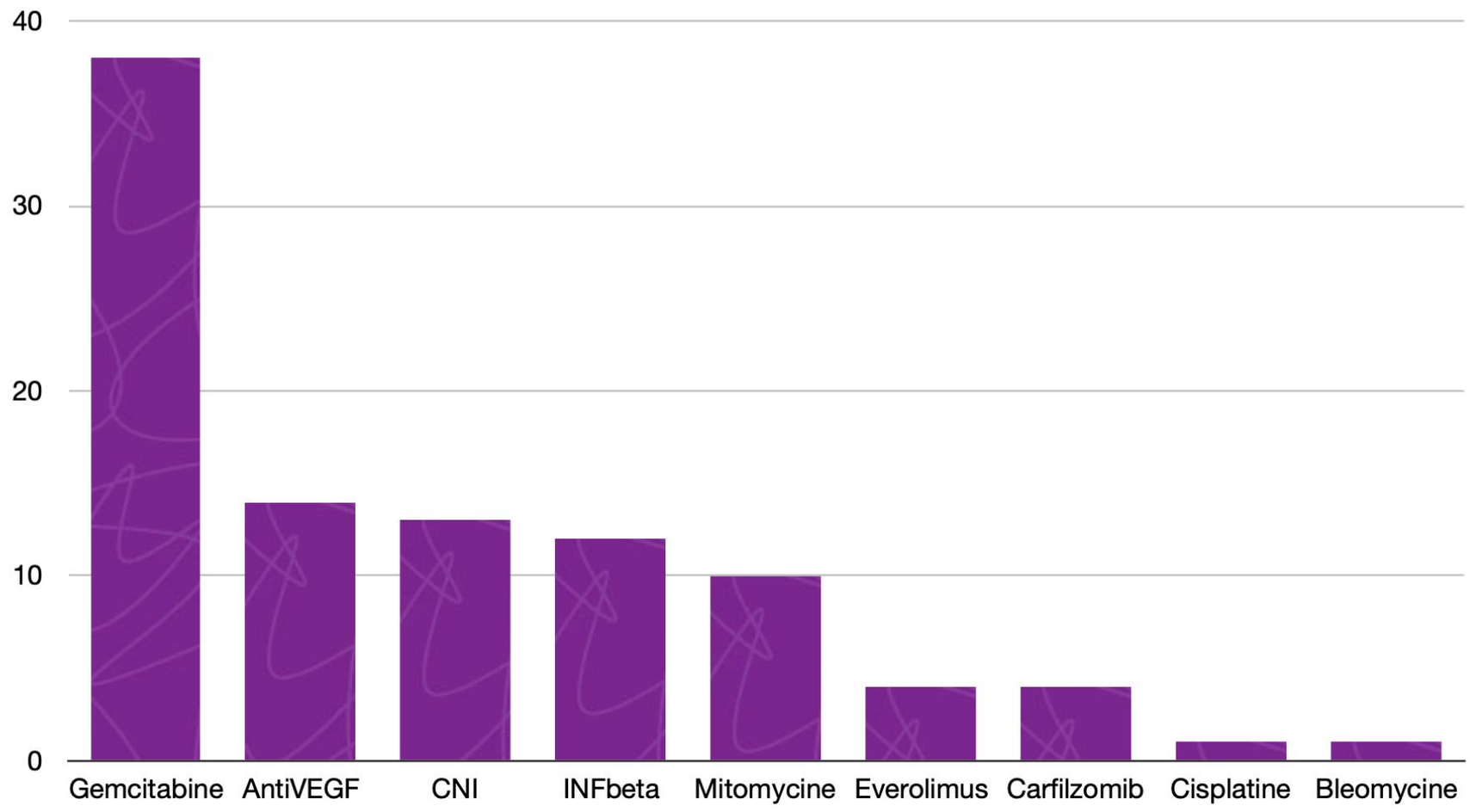
- No guidelines on the treatment which depends on the incriminated drug class -> Importance of obtaining an opinion from Regional Reference Centers

- The data presented today is biased !

- Publication bias (success), simple cases unreported

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

Registre MAT Médicaments
AN 1



Merci à tous !

Toulouse, Bordeaux, Valenciennes, Reims.....

Nephrol Dial Transplant (2017) 32: 466–474
doi: 10.1093/ndt/gfw453
Advance Access publication 20 February 2017

ndt
Nephrology Dialysis Transplantation

Original Article

Eculizumab in secondary atypical haemolytic uraemic syndrome

29 patients with secondary TMAs

Eculizumab if worsening of renal function and persistence of TMA despite the treatment of the TMA-precipitating trigger

22 patients genetic analysis -> Pathogenic variants in 2 (none in DITMA)

Eculizumab discontinued after a median of 8 weeks

Cavero et al. NDT 2017

Table 1. Characteristics at the initiation of eculizumab treatment

	Patients ($n = 29$)
Age (years)[a]	51.8 (36.2–59.6)
Gender, no. (%), male	16 (55.2)
Cause of aHUS, no. (%)	
Drug-induced	**15 (51.7)**
Tacrolimus	14 (93.3)
Everolimus	4 (26.7)
Sirolimus	1 (6.7)
Systemic disease	**8 (27.6)**
SLE	3 (37.5)
Scleroderma	2 (25)
Vasculitis (EGPA)	2 (25)
Antiphospholipid syndrome	1 (12.5)
Other causes	**6 (20.7)**
Pregnancy/postpartum	2 (33.3)
Cancer related	2 (33.3)
Acute humoral rejection renal transplant	1 (16.7)
Primary intestinal lymphangiectasia	1 (16.7)

Cavero et al. NDT 2017

Time from aHUS diagnosis to eculizumab treatment (days)	13 (7–26)
Extrarenal manifestation, no. (%)	11 (37.9)
Dialysis before eculizumab, no. (%)	14 (48.3)
Laboratory findings	
SCr (mg/dL)[a]	4 (3.4–5.6)
eGFR (mL/min/1.73 m^2)[a]	13 (7.7–19.0)
LDH (mg/dL)[a]	960 (570–1950)
Haptoglobin (mg/dL)[a]	5 (0–12)
Haemoglobin (g/dL)[a]	8.8 (8.1–9.9)
Platelet count (×1000/μL)[a]	73 (51–113)
Schystocites, no. (%)	28 (96.6)
Follow-up (months)[a]	5.2 (4.2–14.1)

Cavero et al. NDT 2017

Table 2. Drug-induced aHUS

Patient	Age (years), gender	Offending drug	Treatment before eculizumab	PE no. of sessions
1	43, female	Tacrolimus[a]	DW + PE	3
2	63 female	Tacrolimus[a]	DW + PE	10
3	34, male	Tacrolimus[a]	PE	3
4	18, female	Tacrolimus[a]	DW + PE	2
5	52, female	Tacrolimus[a]	DW	–
6	43, male	Tacrolimus[a]	DW + PE	6
7	36, female	Everolimus[a]	DW + PE	6
8	60, male	Tacrolimus[b]	DW	–
9	67, male	Tacrolimus, everolimus[b]	DW + PE	6
10	59, male	Tacrolimus, everolimus[b]	DW + PE	5
11	65, male	Tacrolimus, everolimus[b]	DW + PE	6
12	51, male	Tacrolimus[c]	DW + PE	2
13	54, female	Tacrolimus, sirolimus[c]	DW + PE	7
14	55, male	Tacrolimus[d]	DW + PE	12
15	42, female	Tacrolimus[e]	DW + PE	3

7 kidney transplants
4 lung transplants
1 liver transplant
1 heart transplant
2 bone marrow transplants

ttt stopped in all
patients but 1 (hyperimmunized)

Kidney biopsies in 18 patients
-> TMA in all biopsies
No acute humoral rejection

Cavero et al. NDT 2017

CNI-induced TMAs

Cyclosporine/tacrolimus

Endothelial dysfunction
- Vasoconstriction
- Release of complement-
activation of microparticles

-> Hypertension/Nephrotoxicity

-> Histological lesions of TMA/Few clinical symptoms

Ttt:
Decrease the dose?
Belatacept?

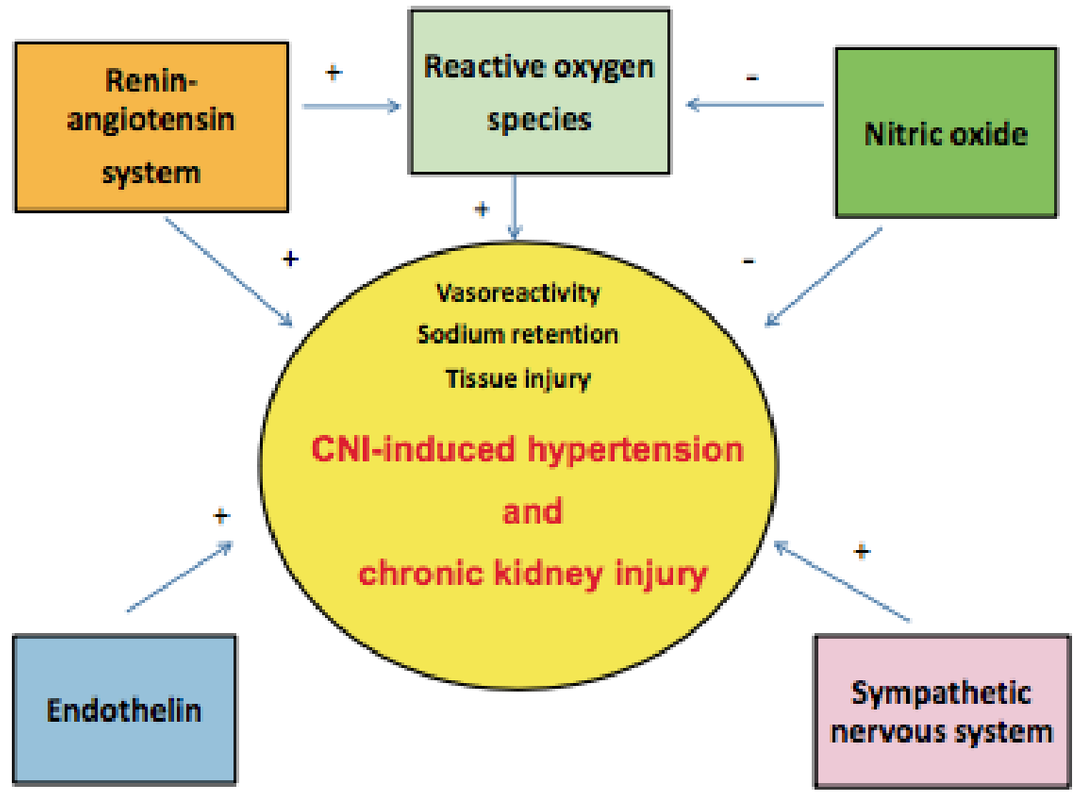


Fig. 2. The major vasoactive systems and their interactions in the development of CNI-induced endothelial dysfunction, hypertension and kidney damage.

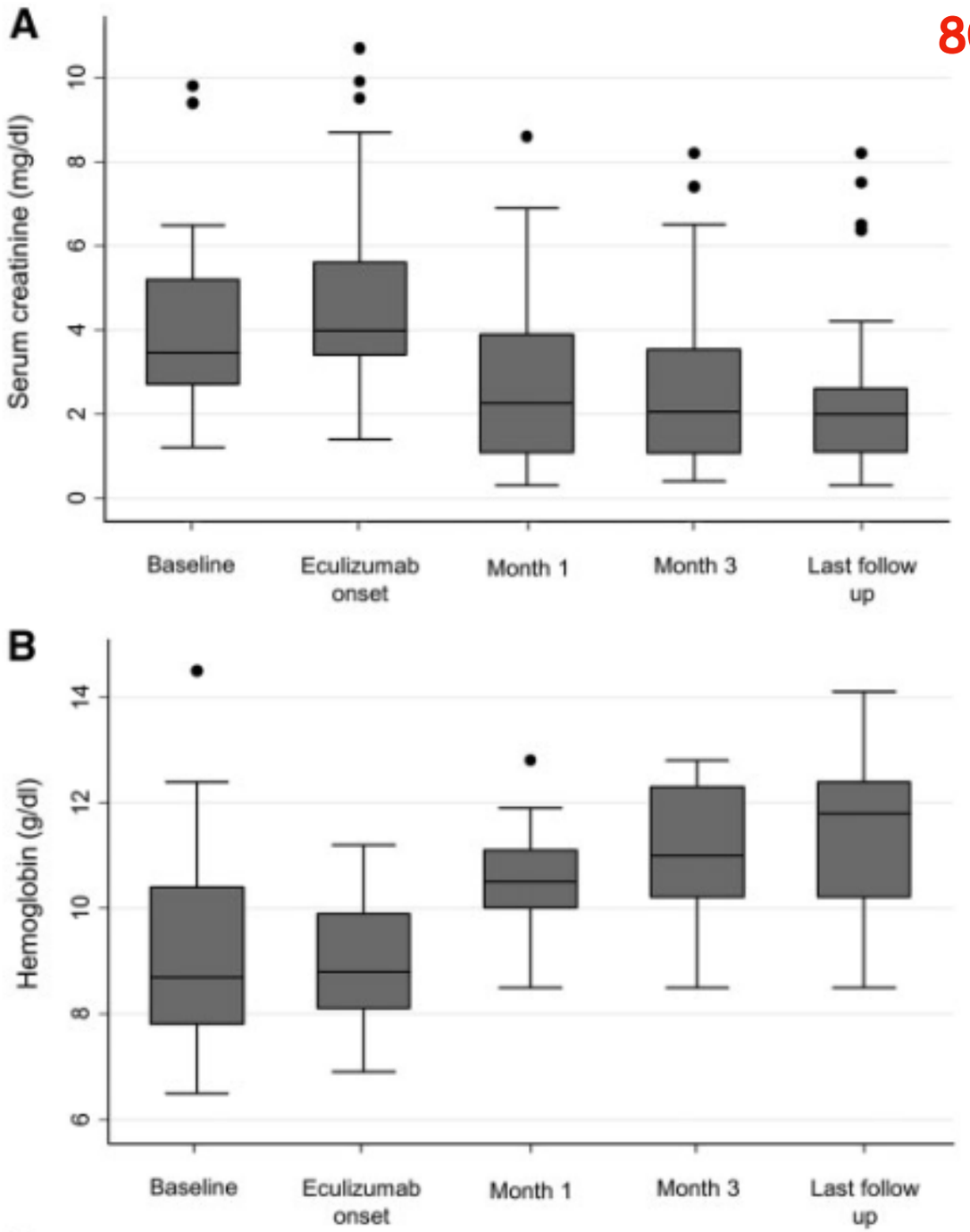
Hoskova et al. Physiol Res 2017
Renner et al. JASN 2013

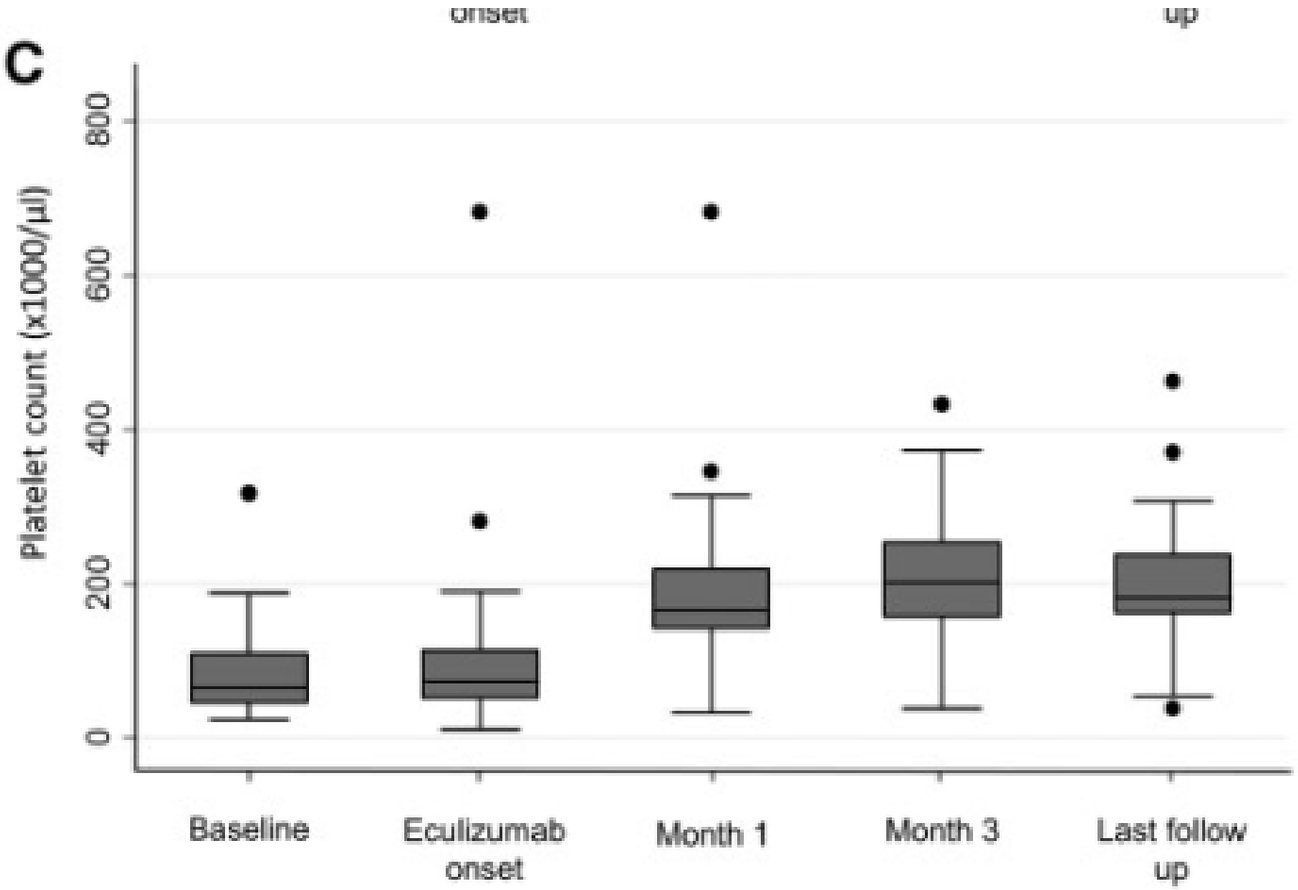
Eculizumab (duration, no. of doses)	Time from aHUS to eculizumab (days)	Highest SCr (mg/dL) HD (Yes/No)	Latest SCr (mg/dL)	Follow-up (months)
2 weeks, 2	4	3.8 No	1.1	16.2
18 weeks, 11	53	3.1 Yes	2.0	5.9
24 weeks, 14	10	9.8 Yes	2.6	6.7
3 weeks, 3	14	2.1 No	2	9.6
8 weeks, 6	26	2.9 No	1.2	8.3
30 weeks, 17	35	3.8 Yes	1.1	16.2
6 weeks, 5	9	4.2 No	2.1	17.5
4 weeks, 4	53	3.4 Yes	2.5	3.4
6 weeks, 5	10	1.8 No	2.0	1.7
10 weeks, 7	7	3.5 No	2.0	4.8
2 weeks, 2	9	3.3 No	2.4	4.5
4 weeks, 4	10	2.4 No	0.6	2.9
3 weeks, 3	7	4.2 Yes	1.2	1.5
18 weeks, 11	27	3.0 No	2.4	14.1
3 weeks, 3	13	1.4 No	0.5	17.0

Cavero et al. NDT 2017

Rapid resolution of the TMA in 20 (68%) patients,
15 of them showing a > 50% serum creatinine reduction at the last follow-up

80% of TMA resolution in patients with DITMA





Cavero et al. NDT 2017

Three-year outcomes in kidney transplant recipients switched from calcineurin inhibitor-based regimens to belatacept as a rescue therapy

Study design

Single center retrospective study (01/2012 to 01/2019)

N=115 kidney transplant recipients converted from CNI to belatacept

Conversion :
- eGFR < 30 ml/min/1.73m²
- Chronic histological lesions
- CNI-induced thrombotic microangiopathy (TMA)

36 months after conversion

Cohort

Leading cause : Chronic histological lesions (56.5%)

33% early (< 3 months)
Delay : 10 (2-27.5) months

Age : 55.8 ± 15 years
eGFR : 31.5 ± 17.5 ml/mn

Preformed DSA : 9.8%
TMA : 19.6%

36-months outcomes

Patient survival : **88%**

Death-censored kidney allograft survival : **92%**

eGFR increase :
31.5 ± 17.5 to 36.7 ± 15.7 ml/min/1.73m²
(p<0.01)

Acute rejection rate : **10.4%**
OI incidence : **5.2 [2.9-7.6] per 100 PY**

De novo DSA : **0%**
TMA : **0%**

Conclusion

Rescue conversion from CNIs to belatacept is safe and beneficial. It could represent a compromise facing organ shortage.

Graphical abstract by @MorelAntoine9

Morel et al., *Transpl. Int.* 2022
doi: 10.3389/ti.2022.10228

ESOT Leading the way in transplantation

Transplant International

GRAPHICAL ABSTRACT |