Thérapie du PTT

Nouveaux enjeux en 2021

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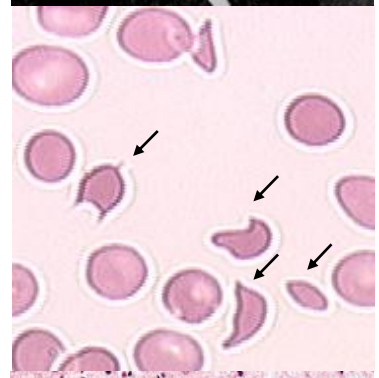
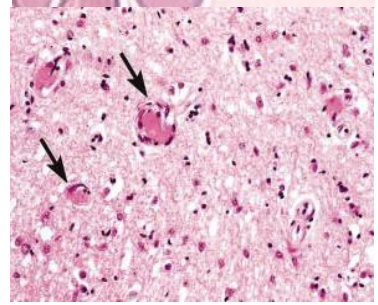
Rencontres en Immunologie et Immunothérapies pratiques - Septembre 2021

TTP: definition – Clinical presentation

- **Microangiopathic hemolytic anemia**
- **Profound peripheral thrombocytopenia (< 30 G/L)**
- **Organ failure of variable severity**
- **Severe ADAMTS13 deficiency**

E. Moschcowitz, 1924





Congenital

(Upshaw-Schulman syndrome)

Neonatal/post neonatal period
Childbearing age women

<0.13 cases / 10^6 hab /y

Immune-mediated

Young women

Fatal

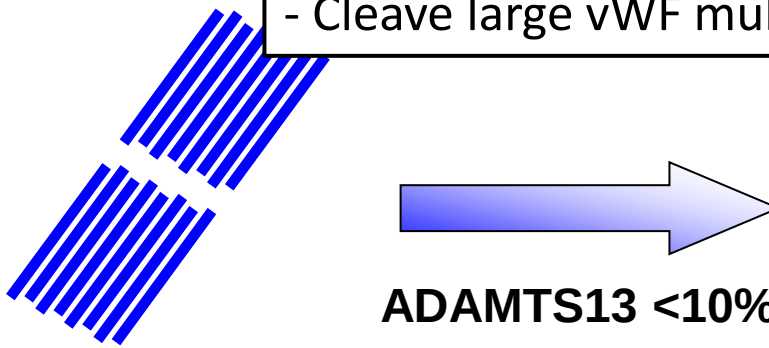
2-3 cases / 10^6 hab /y

> 120 new patients/y in France

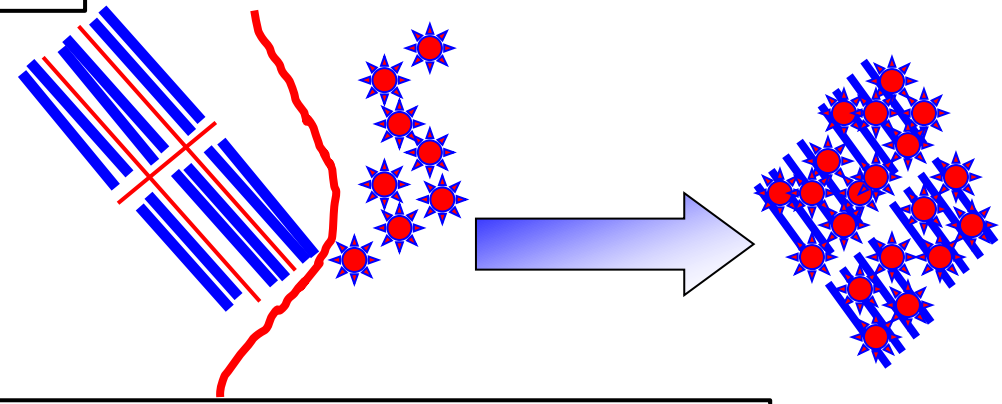
Pathophysiological basis of iTTP treatment

1. Replenish ADAMTS13 levels:
- Saturate anti-A13 Abs
- Cleave large vWF multimers

Very large volumes of plasma (TPE) (exogenous A13)

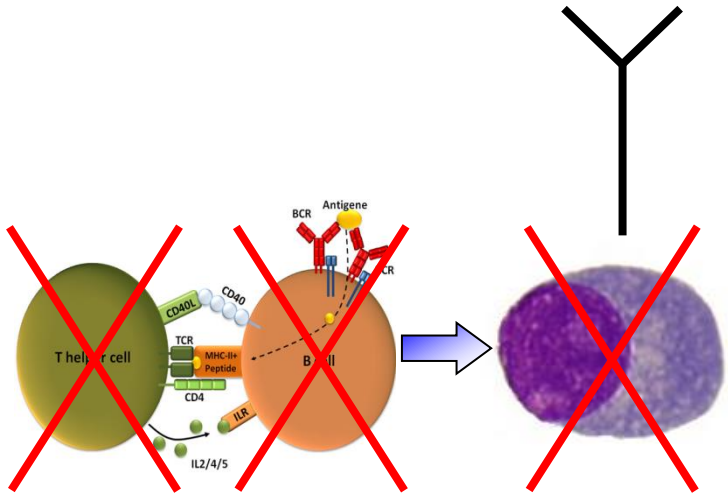


ADAMTS13 <10%



3. Inhibition of platelet-vWF interaction

- Inhibitors of vWF-gp1b axis



2. Immunomodulation

- Target specifically B-cells (rituximab)
- Target T-cells (cyclosporine A)
- Target plasma cells (bortezomib)
- Other non specific immunosuppressors: steroids, CPM, VCR…, splX

Historical treatment of iTTP

Vol. 325 No. 6 PLASMA EXCHANGE VS. PLASMA INFUSION FOR TTP — ROCK ET AL. 393

COMPARISON OF PLASMA EXCHANGE WITH PLASMA INFUSION IN THE TREATMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA

GAIL A. ROCK, PH.D., M.D., KENNETH H. SHUMAK, M.D., NOEL A. BUSKARD, M.D., VICTOR S. BLANCHETTE, M.D., JOHN G. KELTON, M.D., RAMA C. NAIR, PH.D., ROBERT A. SPASOFF, M.D., AND THE CANADIAN APHERESIS STUDY GROUP*

398 THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 8, 1991

IMPROVED SURVIVAL IN THROMBOTIC THROMBOCYTOPENIC PURPURA–HEMOLYTIC UREMIC SYNDROME

Clinical Experience in 108 Patients

WILLIAM R. BELL, M.D., HAYDEN G. BRAINE, M.D., PAUL M. NESS, M.D., AND THOMAS S. KICKLER, M.D.

Daily therapeutic plasma exchange + steroids in emergency until remission = core treatment of TTP

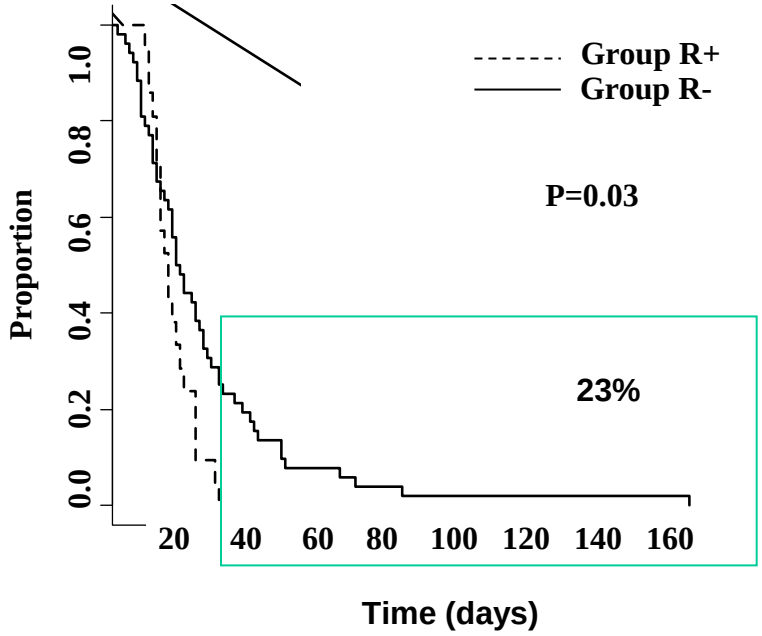
With this regimen, prognosis was outstandingly improved

Remission/survival could reach 85%, vs almost no survival before

Rituximab in acute iTTP to hasten recovery

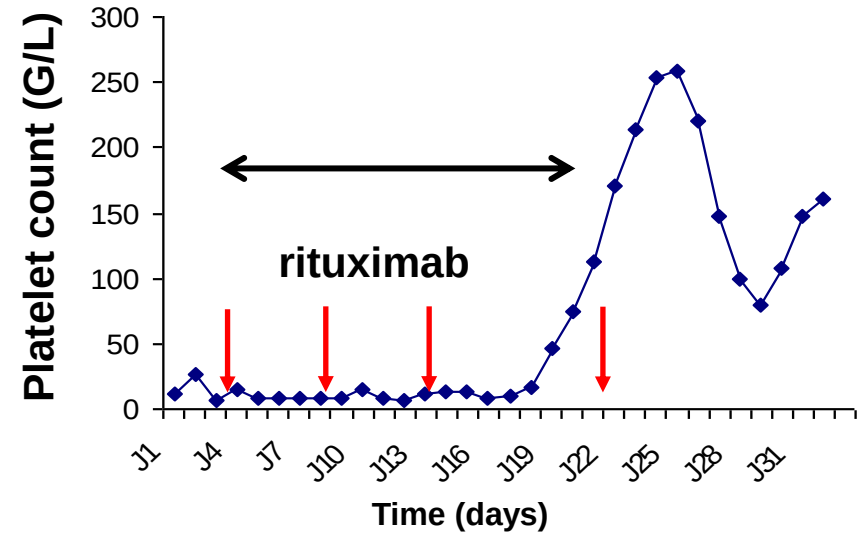
First as a salvage therapy, then frontline…

Rituximab prevents slow responses to TPE



Rituximab limits the duration of TPE treatment

Rituximab is not efficient in real time



Mean time to platelet count recovery after the first rituximab infusion: 12 ± 6.7 d

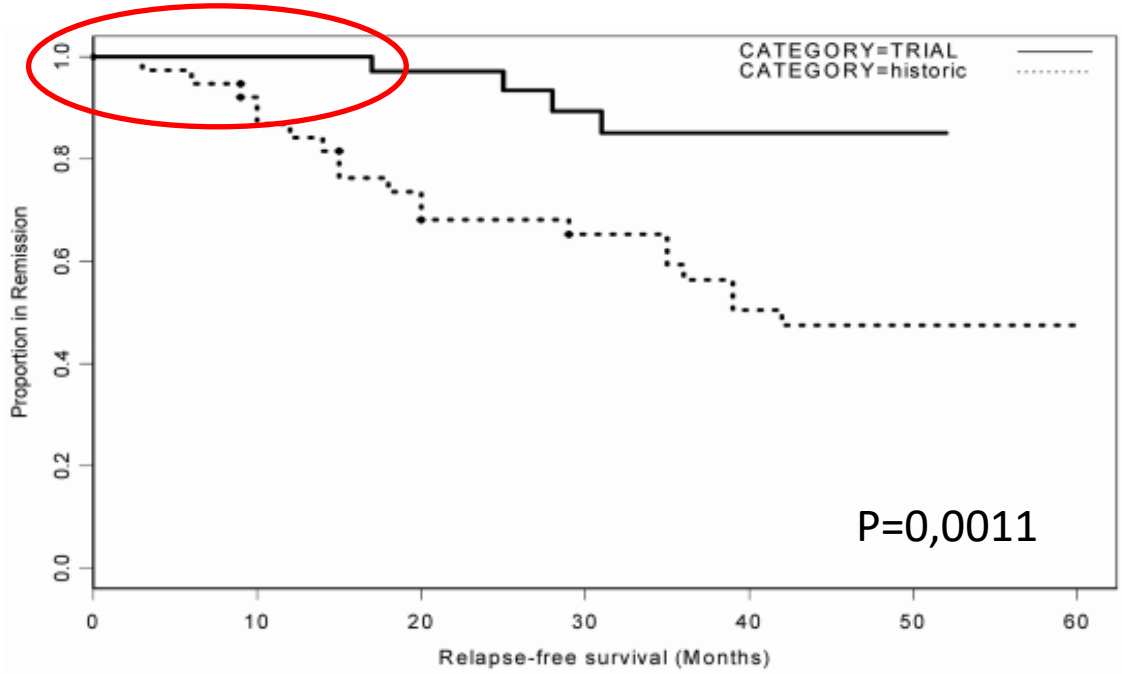
Scully et al., Br J Haematol 2007; CNR-MAT, Crit Care Med 2012

Rituximab and iTTP: for the best and (not) for worse

Should all patients receive rituximab front-line???

Scully et al., Blood 2011

Risk of overtreatment for a significant nb of patients at the acute phase….. but patients are remarkably protected from relapses for 12-18 months

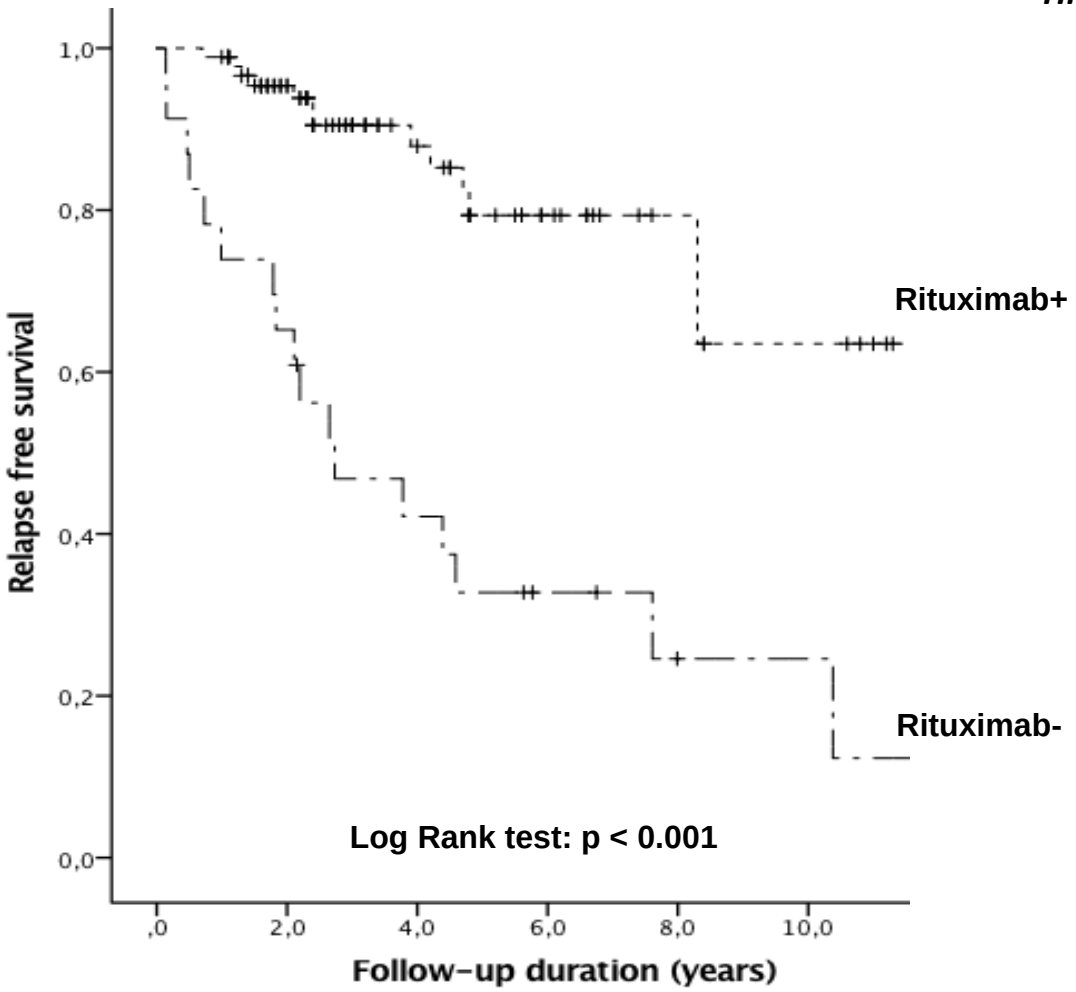


40% of patients w/o RTX remain with an undetectable (<10%) ADAMTS13 activity after the acute phase, and

40% others remain with a decreased (10-50%) activity: those patients are prone to relapse

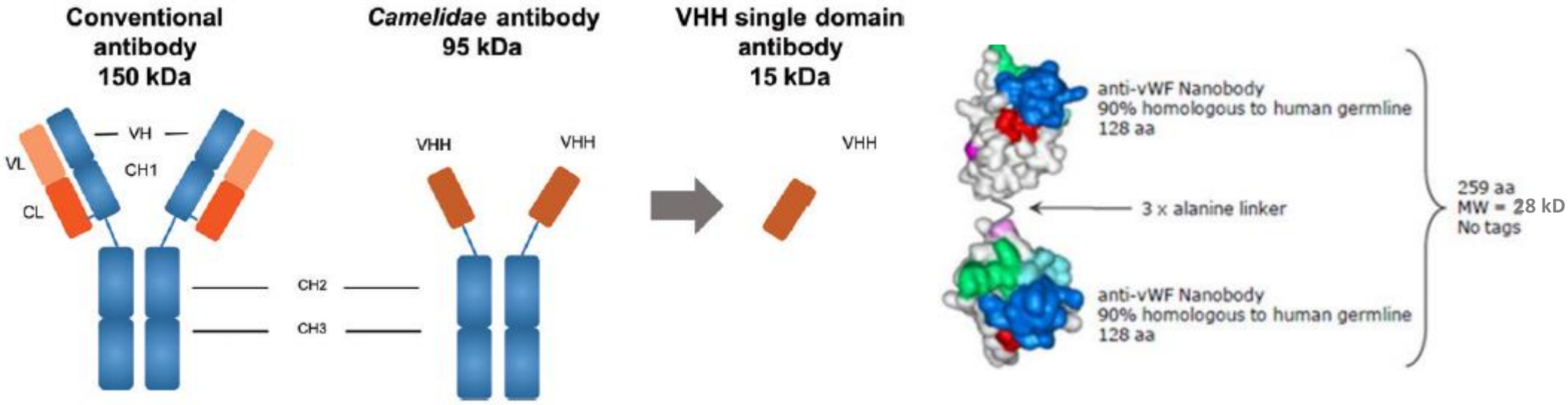
Rituximab: the guardian angel of ADAMTS13

Hie et al., Blood 2014; Jestin et al., Blood 2018

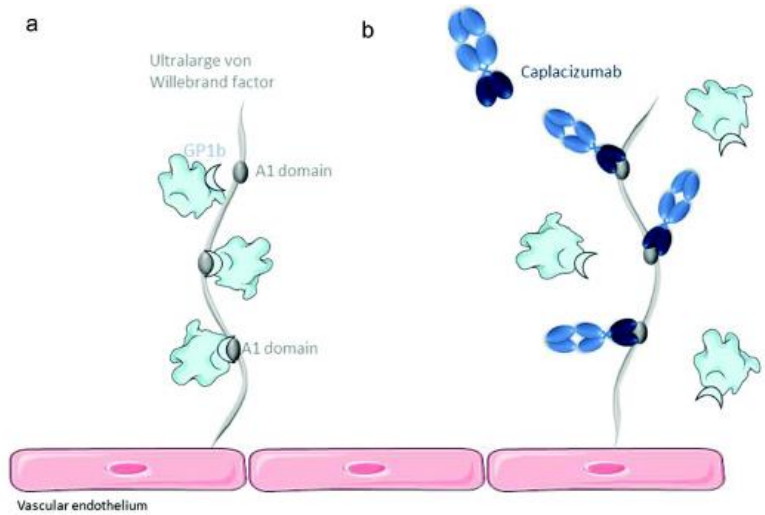


- Without preemptive treatment: 17/23 clinical relapses (74%) (multiple in 11) after a median follow-up of 7 y;
- Cumulative incidence of relapse: 0.26/y

Caplacizumab: a small antibody with big implications for iTTP



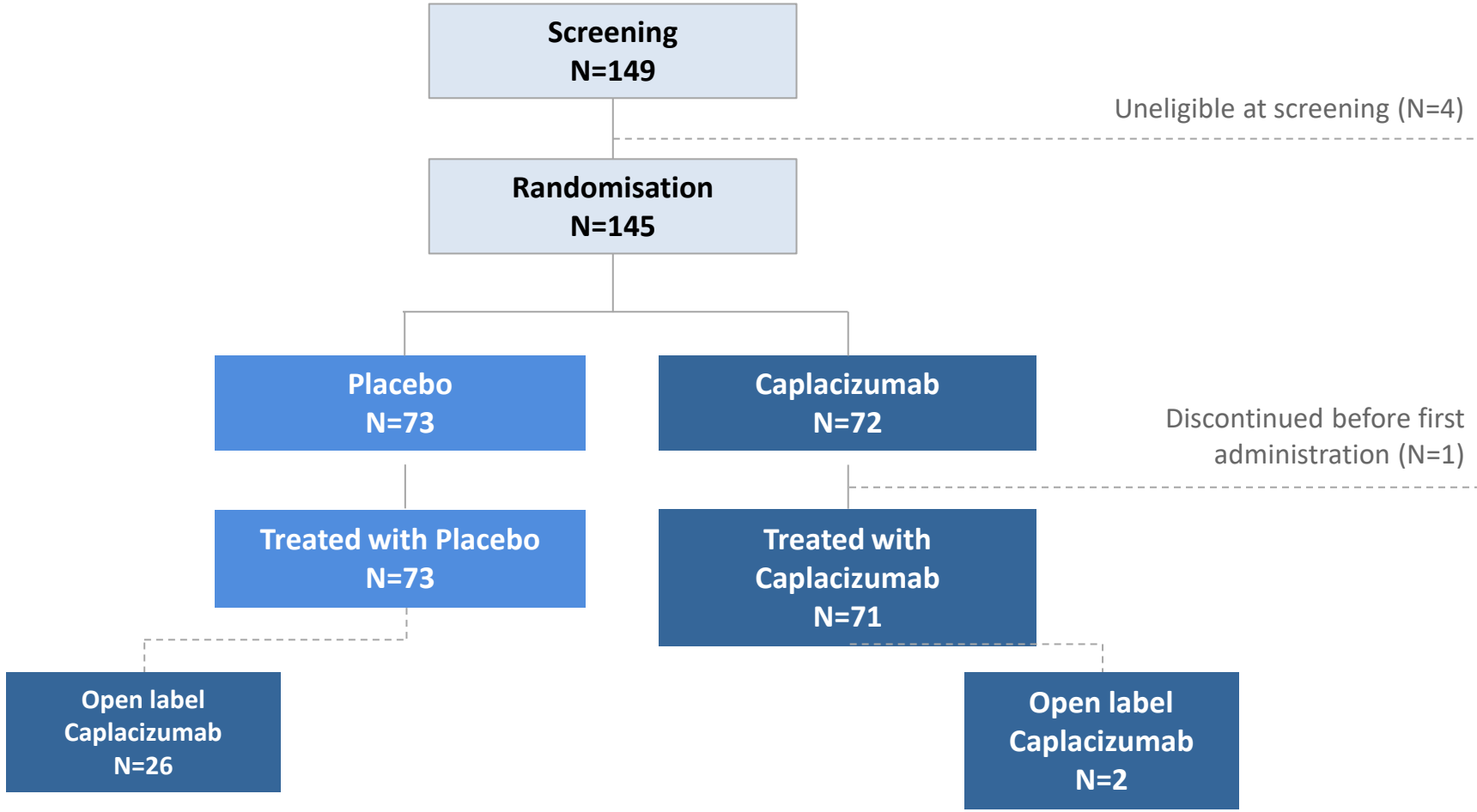
Therapeutic class of proteins derived from the heavy-chain variable domains that occur naturally in heavy-chain Ig from *Camelidae*



Poullin et al., Drugs of Today, 2019

A new player in the game: the anti-vWF nanobody caplacizumab in TITAN and HERCULES trials

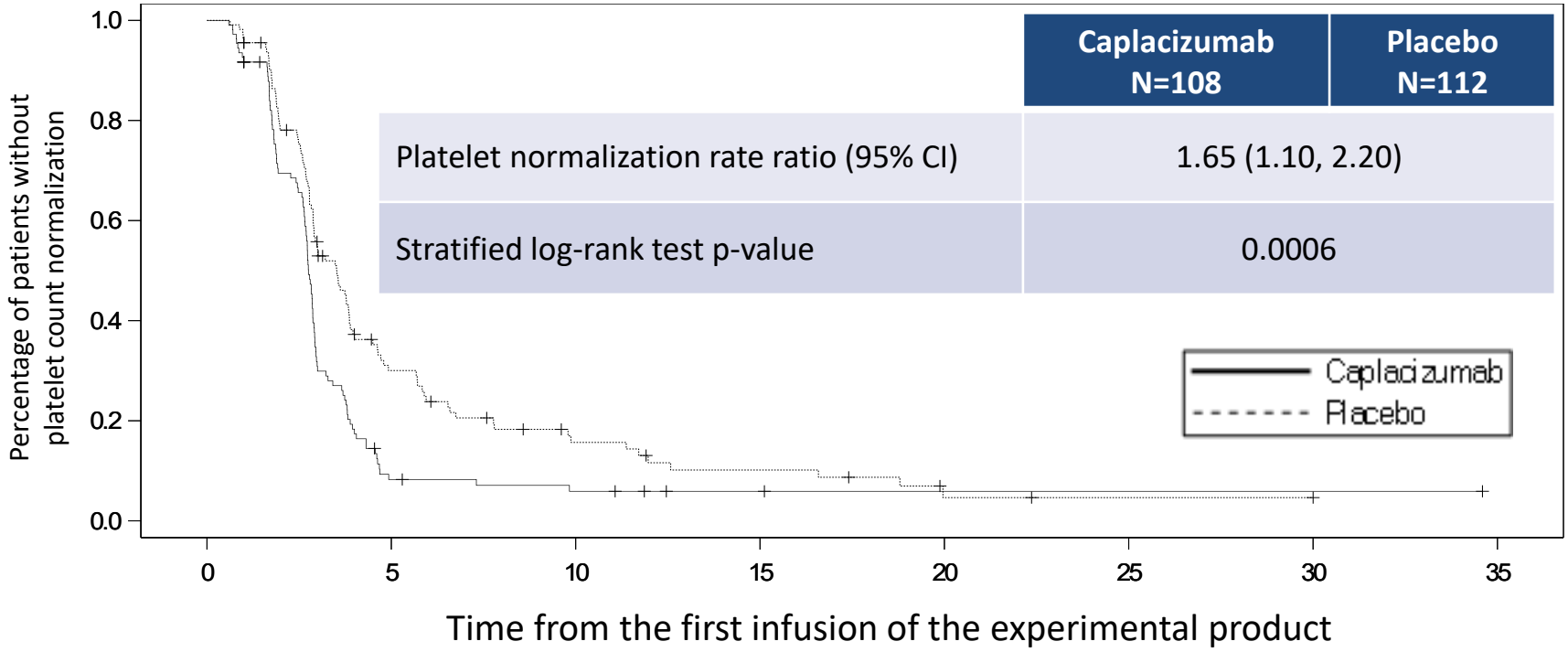
Flow chart (HERCULES):



Scully, Cataland, Peyvandi, Coppo et al., N Engl J Med 2019

Primary endpoint: time to first platelet count recovery

Integrated analysis (TITAN + HERCULES):

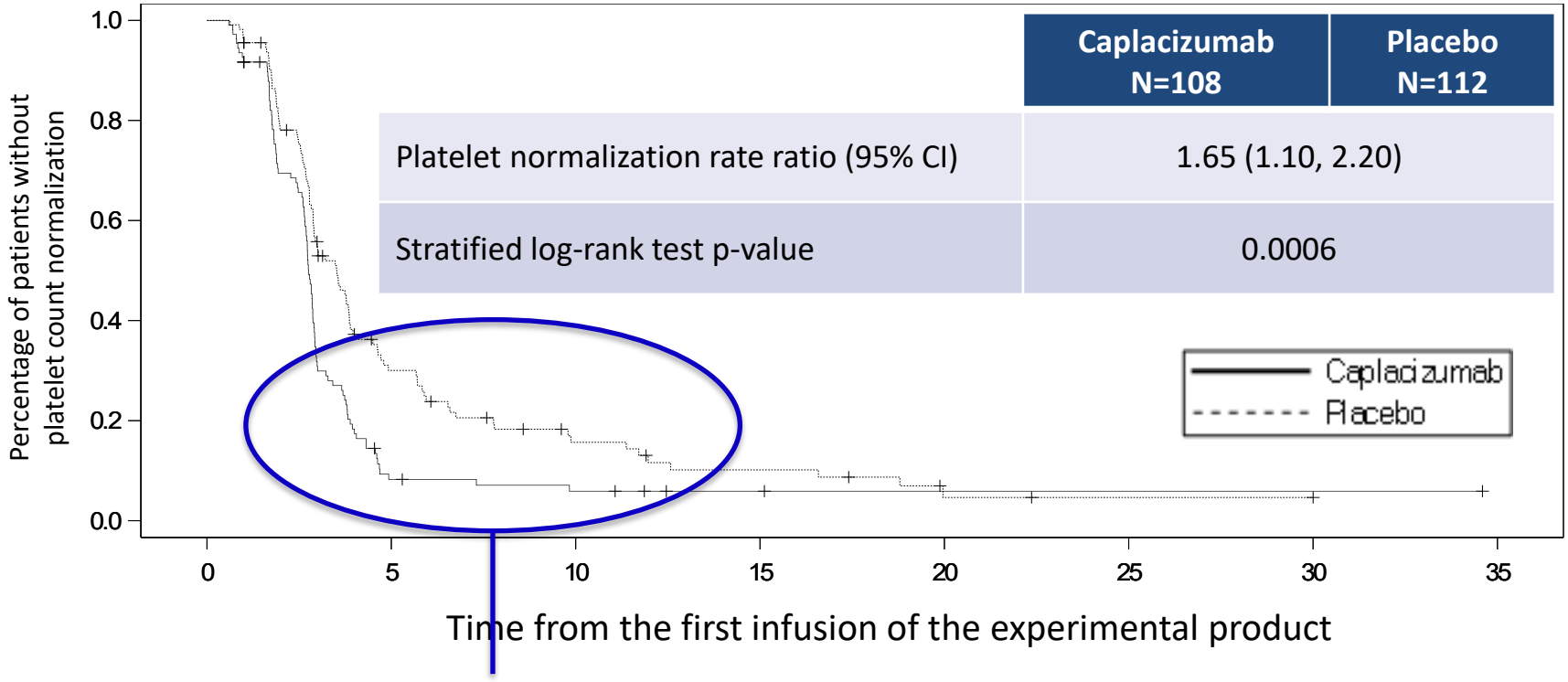


Less exposure to thrombocytopenia = less exposure to death

Scully, Cataland, Peyvandi, Coppo et al., N Engl J Med 2019

Primary endpoint: time to first platelet count recovery

Integrated analysis (TITAN + HERCULES):



Caplacizumab makes a bridge until rituximab efficacy

Scully, Cataland, Peyvandi, Coppo et al., N Engl J Med 2019

Composite criteria – Death, recurrences and major TEE

TITAN + HERCULES (integrated analysis)	Caplacizumab N=108	Placebo N=112
Total number of patients with at least 1 event, n (%)	**14 (13.0)**	**53 (47.3)**
TTP-related death	0	4 (3.6)
Exacerbations	6 (5.6)	39 (34.8)
Major thromboembolic events	8 (7.4)	14 (12.5)
p-value	**<0.0001**	
Refractoriness – n (%)	**0 (0.0)**	**7 (6.3)**
95% CI	NA	(2.5, 12.5)
p-value	**0.0089**	

Less death/refractoriness; impressively less exacerbations = platelet count improvement is durable

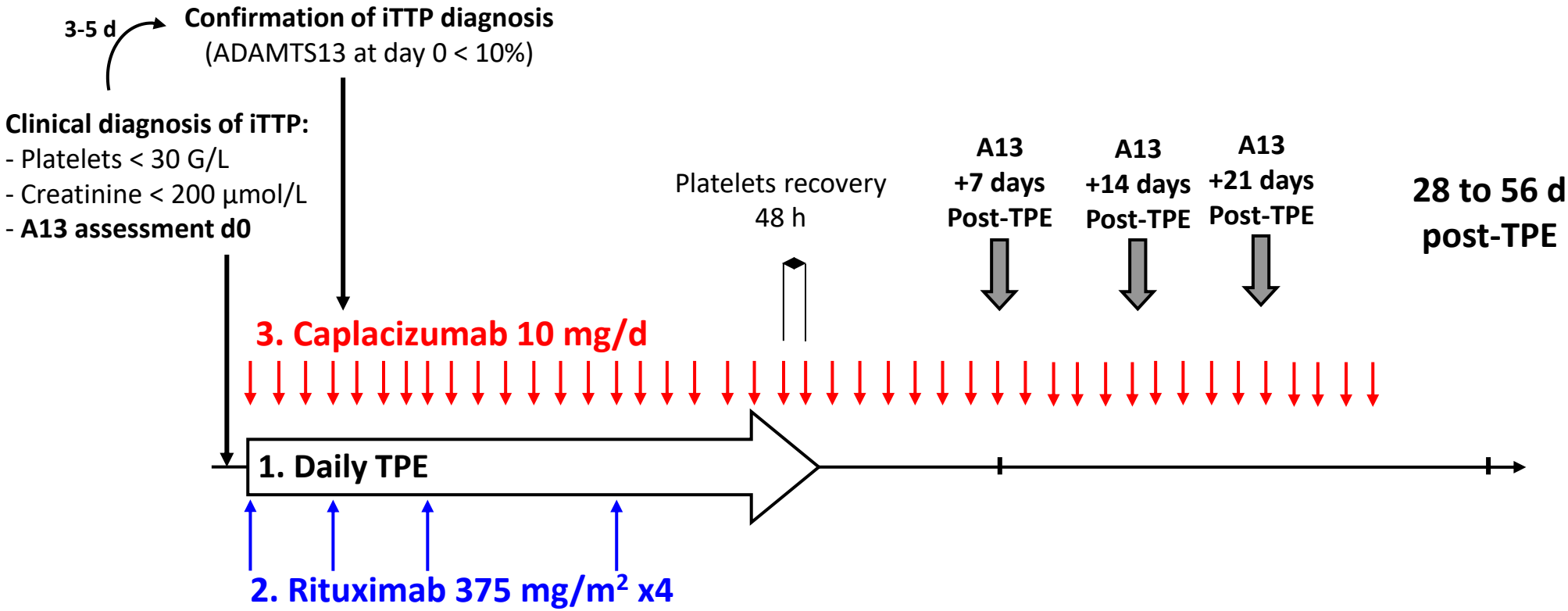
Scully, Cataland, Peyvandi, Coppo et al., N Engl J Med 2019

Caplacizumab after the Greec epic: where do we stand?

National therapeutic recomendation for an homogeneous use of caplacizumab during the early access program

The Caplavie regimen: a triplet TPE – Corticosteroids/Rituximab - Caplacizumab

N=90 patients recruited within 18 months *vs* 180 historical patients



Primary and Secondary Outcomes According to the Treatment Regimen

Outcome	Triplet regimen (N = 90)	Historical cohort (N = 180)	*P* - value
Primary outcome[1]			
Composite of death and refractoriness			
All patients	**2 (2.2%)**	**22 (12.2%)**[a]	**0.01**
According to French Severity score:			
0–2	2 (2.8%)	15 (8.3%)	<0.01
3–4	0	7 (33%)	
Secondary outcomes[1]			
Death	**1 (1.1%)**	**12 (6.7%)**	**0.06**
Refractoriness	**1 (1.1%)**	**16 (18%)**[b]	**0.01**
Exacerbations	**3 (3.4%)**	**70 (44%)**	**<0.01**
Time to durable platelet count recovery	5 (4–6)	12 (6–17)	<0.01
Number of daily TPE until remission	5 (4–7)	10 (6–16)	<0.01
Volume of plasma (Liter) until remission	24.2 (18.3–30.2)	44.4 (26.3–74.3)	<0.01
Time to ADAMTS13 activity >20% (days)	28 (14–42)	48 (24–83)	<0.01
Length of hospitalization (days)	13 (9–19)	22 (15–30)	0.01

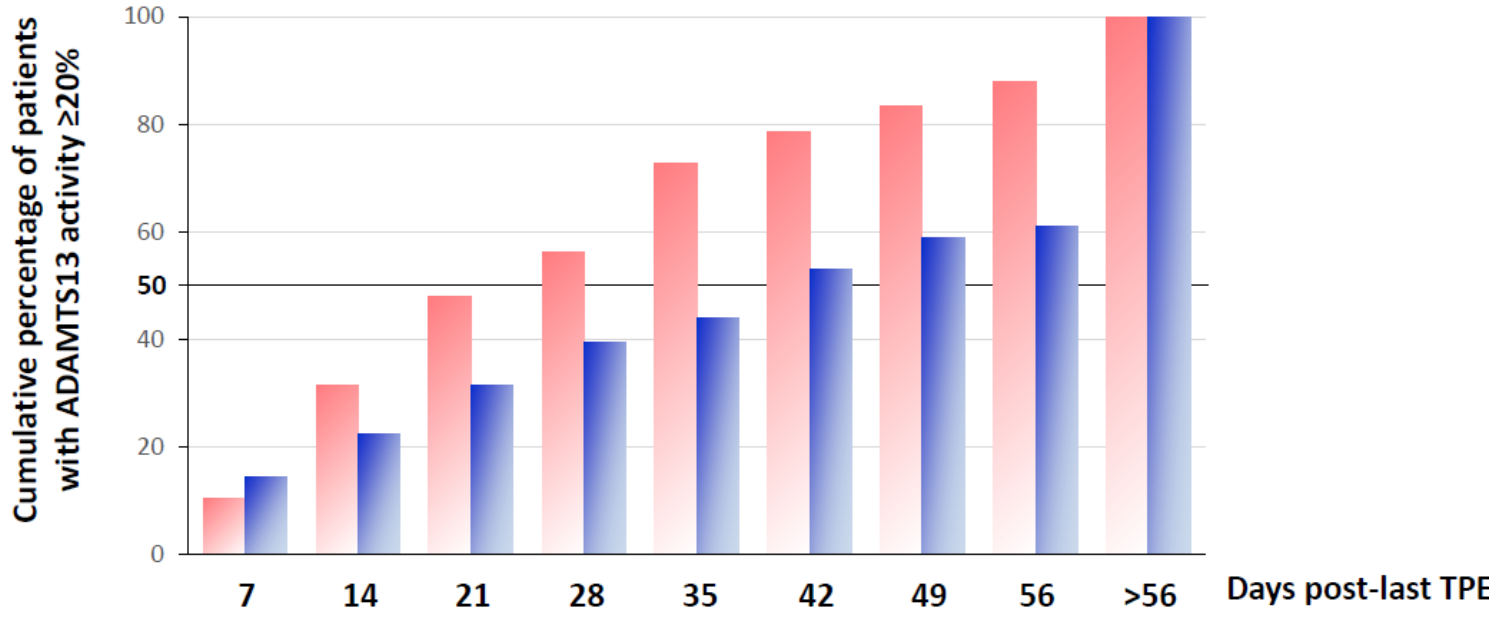
Better prognosis

↓ Burden of care

(a) 1 death in triplet regimen cohort: 83 year-old woman - cardiac involvement (cardiac troponin I, 0.51 µg/L); no cerebral involvement; LDH 1433 U/L; received 3 RTX, caplacizumab on day 1; had exacerbation on Day 5; died on Day 9 of a probable PE with cardiogenic shock despite salvage thrombolysis.

Coppo et al., Blood 2021

Time to ADAMTS13 Improvement (> 20%)



Triplet regimen cohort

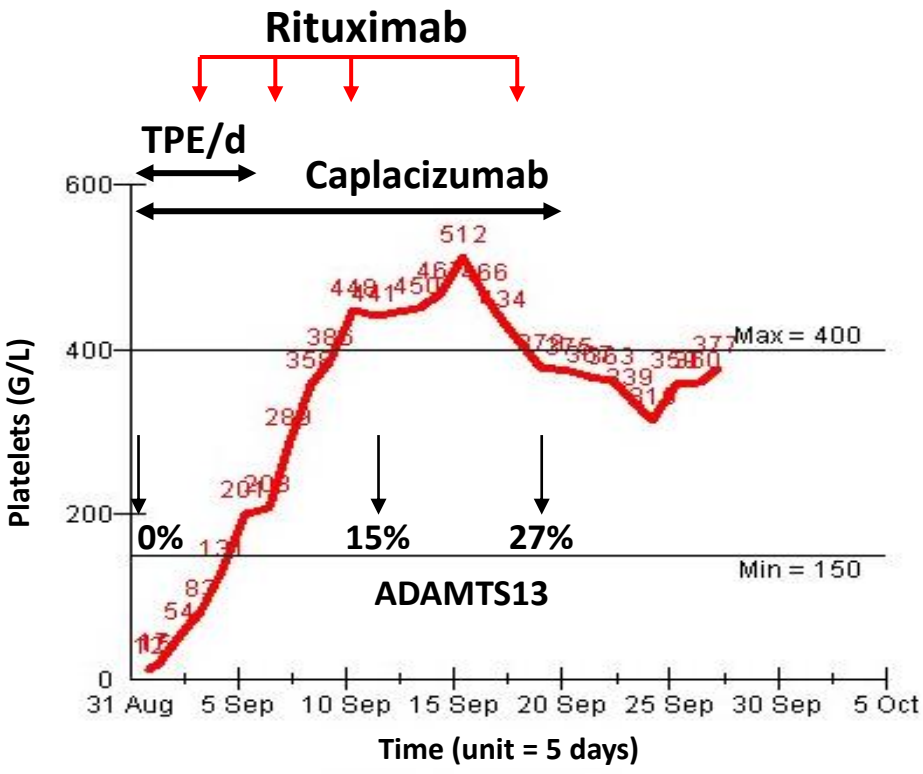
Historical treatment cohort

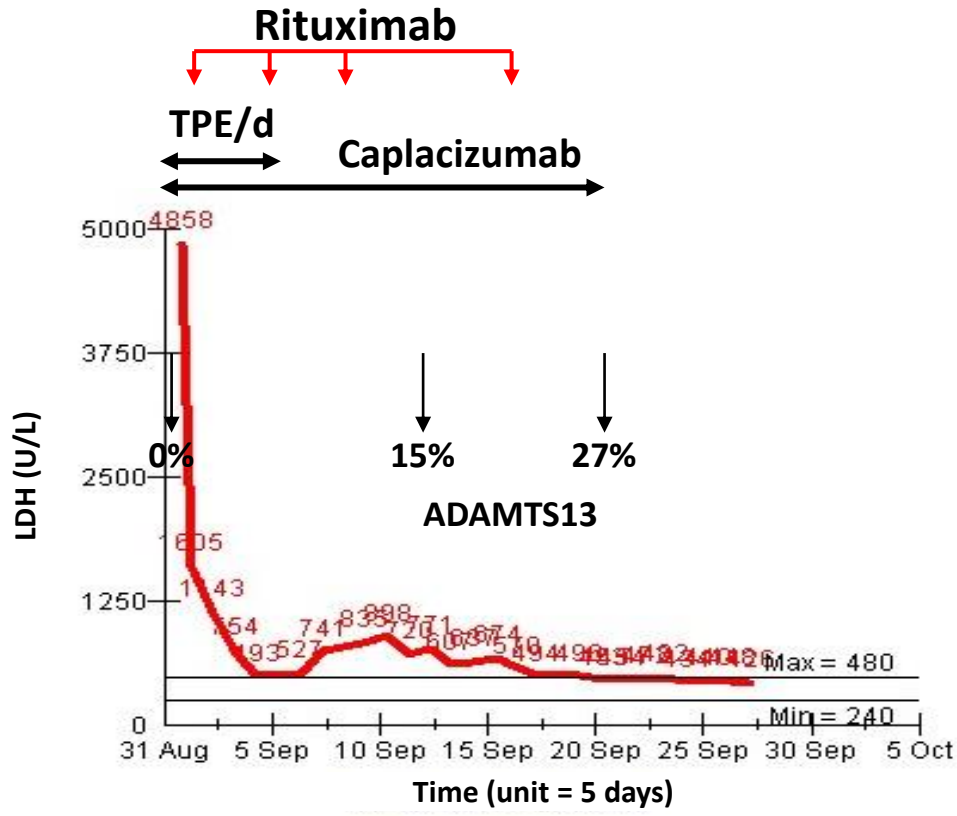
10% in the triplet regimen improve ADAMTS13 activity > D56…

Coppo et al., Blood 2021

Patient Case

45-year-old woman - CNS+/Heart+; French score = 2





< 7 days of TPE and ICU stay – No exacerbation – Caplacizumab stopped when A13 > 20%
Caplacizumab could negativate the worse prognosis of cerebral and cardiac involvement

P. Coppo, personal data

Caplacizumab-Related Adverse Events

A total of 46 (51%) patients experienced at least one drug-related adverse event in the triplet regimen cohort[1]

Characteristic	Number of adverse events	Description
Major bleeding	2	1 hemorrhagic shock* with lower digestive bleeding 1 abundant menorrhagia with a decrease in hemoglobin level of 2.5 g/dL
Clinically relevant non-major bleeding	11	3 macroscopic gastrointestinal hemorrhage 7 epistasis 1 subcutaneous hematoma larger than 25 cm^2
Non-clinically relevant non-major bleeding	17	9 ecchymosis or small hematoma 6 gingival bleedings 2 catheter site hemorrhage
Inflammatory reaction	6	Inflammatory swelling at the injection site, especially at the end of the treatment course
Thrombocytosis	19	Platelet count ($x10^3/mm^3$): >450–600: 11 cases >600–900: 7 cases >900: 1 case

* Favorable after RBC transfusion (6 packs) + local hemostasis (no transfusion of VWF/FVIII)

Context: 70 yo; under plavix; chronic renal failure (GFR 20 ml/mn); post-TPE period. ADAMTS13 still undetectable; immunosuppressive treatment optimized[2]

Coppo et al., Blood 2021

The next future

A new hope: the recombinant ADAMTS13?

- Phase 1 multicenter, open-label, dose-escalation study in 15 patients with hereditary ADAMTS13 deficiency
- Objectives
  - Safety and immunogenicity
  - Pharmacokinetics
- 3 rADAMTS13 dose cohorts : each received a single injection of 5, 20, or 40 U/kg

- Safe and well tolerated over a dose range of 5-40 U/kg in cTTP patients
- No serious adverse events
- All immunogenicity tests negative for all subjects

- BAX 930 antigen & activity PK parameters were comparable to those estimated from FFP studies
- Demonstrated dose proportionality
- Evidence for BAX 930 activity
  - Effects on platelet count
  - VWF 176 kDa cleavage product

Scully et al., Blood 2017

The next future: a PEX-free regimen?

BRIEF REPORT

Jth

Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab

Linus A. Völker[1,2] | Paul T. Brinkkoetter[1,2] | Paul N. Knöbl[3] | Miroslav Krstic[4] | Jessica Kaufeld[5] | Jan Menne[5] | Veronika Buxhofer-Ausch[6] | Wolfgang Miesbach[7]

[1]Department II of Internal Medicine and Center for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital Cologne, University of Cologne,

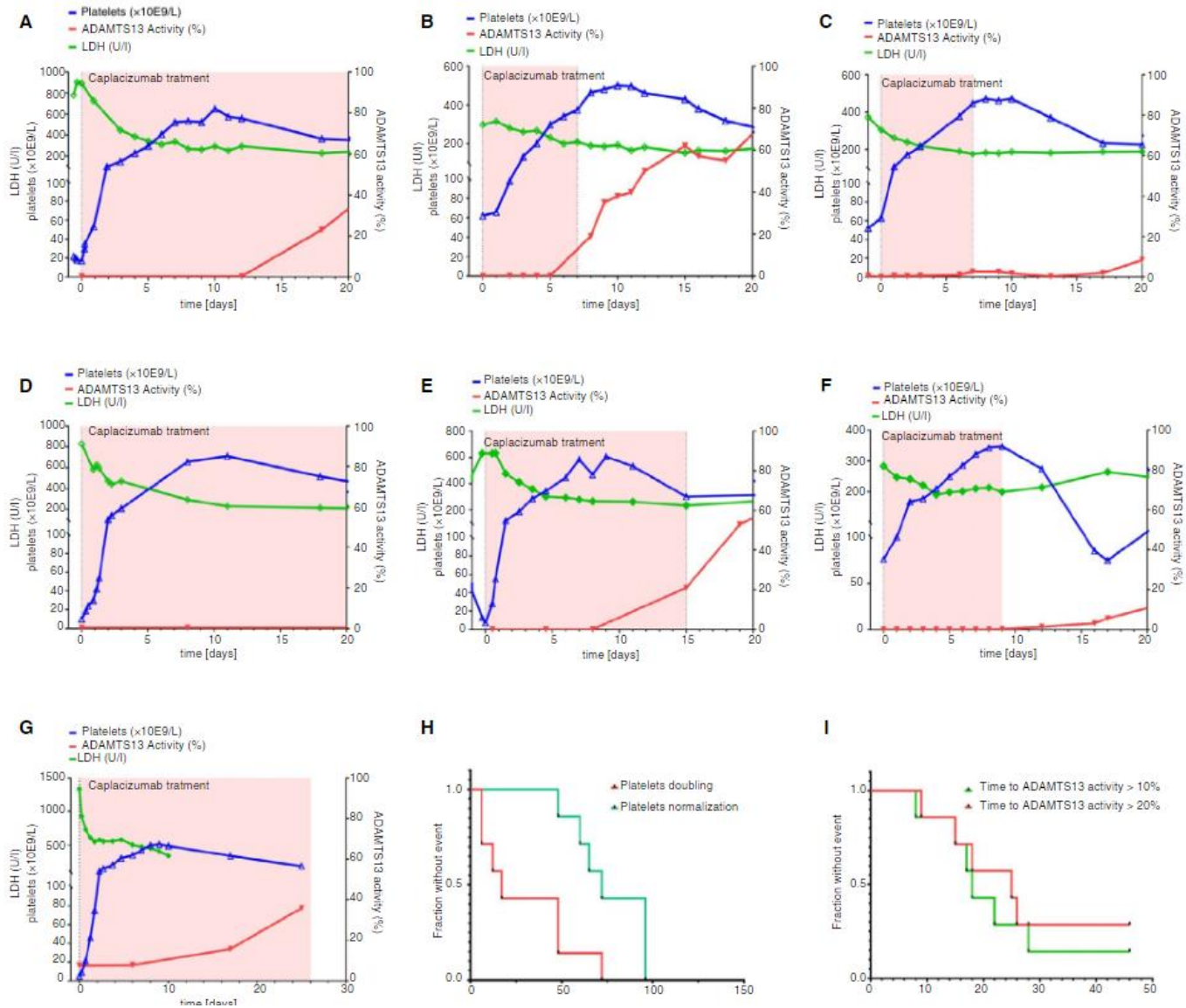
Abstract

Background: Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, life-threatening autoimmune thrombotic microangiopathy. Current standard of care is

Baseline features

	Patient 1 (A)	Patient 2, 1st episode (B)	Patient 2, 2nd episode (C)	Patient 3 (D)	Patient 4 (E)	Patient 5 (F)	Patient 6 (G)	Median (IQR)	Percent (%)
Age at diagnosis, years	25	31	31	46	34	62	75	40.0 (31.8-58)	
Sex	Female	Female		Female	Female	Female	Female		6/6 (100%)
Relapse of known TTP	No	Yes	Yes	Yes	No	Yes	Yes		5/7 (71.4%)
BMI, kg/sqm	27.7	37.0	37.0	35.9	25.7	25.0	32.8	30.3 (26.2-35.1)	
Race	Caucasian	Caucasian		Caucasian	Caucasian	Caucasian	Caucasian		6/6 (100%)
Reason for omission of plasma exchange	Patient refused central line	Oligo-symptomatic and patient	Oligo-symptomatic and patient decision	Oligo-symptomatic and patient decision	Poor venous access	Oligo-symptomatic and patient decision	Poor venous access		
Neurologic symptoms	Facial paresthesia, aphasia	None	None	None	Aphasia, cephalgia, large acute infarction, multiple small non-recent infarctions	None	Yes, unspecified		3/7 (42.9%)
Renal involvement	Proteinuria, high creatinine	None	None	Proteinuria, high creatinine	Proteinuria, high creatinine	None	Proteinuria		4/7 (57.1%)
Cardiac Involvement	None	None	None	None	High troponin (>5 x ULN)	None	High troponin (>2 x ULN)		2/7 (28.6%)
Initial platelet count, G/L	17	62	63	10	7	76	5	17 (8.5-62.5)	
Initial LDH, U/L	902	298	305	828	632	283	1336	632 (301-865)	
Maximum anti-ADAMTS13 inhibitor, unit as indicated[a]	73 U/mL	99 U/mL	57 U/mL	99 U/mL	4 BU/mL	45 U/mL	7.27 BU/mL		
No. of caplacizumab doses	13	8	8	109 (ongoing)[b]	11	10	26	11 (9-19.5)	
Additional Treatments	GC, RTX	GC	GC	GC, RTX	GC, RTX	GC	GC, RTX		GC: 100% RTX: 57.1%

Response to a PEX-free regimen



Systematic improvement of platelet count/LDH level

Duration of treatment with caplacizumab variable; sometimes stopped while A13 <20%

No data on possible neurocognitive sequelae

Unexpected consequences of the absence of plasma?

Towards more precision medicine to improve iTTP prognosis

1. Death rate of acute iTTP scarcely changed for > 20 y. Most deaths occur in the first days of the management; these patients need new strategies efficient immediately

2. Targeted therapies based on anti-vWF agents and rADAMTS13, should help in decreasing TTP early mortality, and the burden of care+++

3. Caplacizumab frontline, in association with immunosuppression and TPE, nicely prevents unfavorable outcomes in iTTP; next step: to monitor ADAMTS13 activity to personalize caplacizumab regimen

4. These new therapies were derived from a better understanding of TTP pathophysiology, reflecting a shift from empiricism to targeted therapies

5. Alleviated therapeutic regimens (TPE-free) should be evaluated, in the next future

The CNR-MAT

Consortium PROFILE (H2020)

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

filière de santé
maladies rares
Reconnue par le Ministère de la Santé

PROFILE