TTP: diagnosis and current management

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Reference Center for Thrombotic Microangiopathies

cnr-mat

ERKNet/ERA webinar – 20 December, 2022

Conflits of interest

SANOFI, ALEXION, TAKEDA, NOVARTIS, JANSSEN

Member of advisory boards

Honoraria for symposiums

Research grants

Clinical case

A 46-yo woman is admitted to the emergency room for purpura, bruises, and a transient weakness of left arm.
She has a past history of overweight and autoimmune thyroiditis. She originates from West Indies.
Neurological examination is unremarkable at admission.

Hemoglobin	9 g/dL
Platelet count	7 K/L
Reticulocytes	135 K/L
LDH level	2xN
Unconjugated bilirubin	1.5xN
Haptoglobin	< normal
Serum creatinine	150 µmol/L (1.7 mg/dL)
B-HCG	Negative
HIV	Negative

ADAMTS13 activity and anti-ADAMTS13 antibodies were sampled and will be available within 5 days.

Which of the following items are correct?

1. The French score of this patient is consistent with a TTP

2. The French score of this patient is consistent with an HUS

3. This patient should receive daily PEX + corticosteroids from day-1

4. This patients should receive daily PEX + corticosteroids / rituximab + caplacizumab from day-1

5. Caplacizumab should be started after ADAMTS13 activity confirms TTP diagnosis

TTP: definition – Clinical presentation

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

Congenital

(Upshaw-Schulman syndrome)

Neonatal/post neonatal period
Childbearing age women

< 0.13 cases / 10^6 hab /y

Immune-mediated

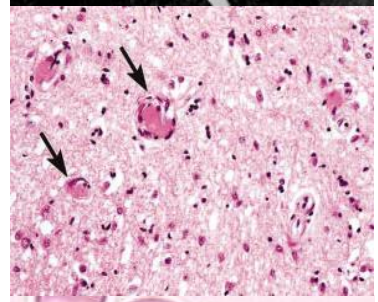
Young women

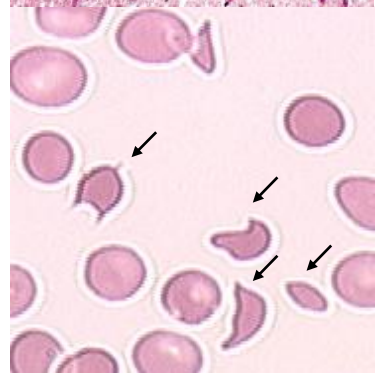
Fatal

1-2 cases/10^6 hab/y

> 120 new patients/y in France

E. Moschcowitz, 1924





Diagnostic issues in TTP

Do not miss the diagnosis+++, that must be done rapidly:

A rapid diagnosis + an adapted treatment => > 95% survival

Diagnosis missed and/or inadequate management => 90% death…

Most of current deaths by TTP result from a diagnostic delay; death has become exceptional once treatment is started+++

To make clinicians aware of TTP diagnosis with simple algorithms is a major goal for rare, spontaneously fatal diseases, but of (very) good prognosis under treatment

An issue nicely illustrated by TTP+++

1. iTTP: clinical presentation

	CNR-MAT, 2010 (N = 160)	*Kremer Hovinga et al. 2010 (N = 60)*	*Veyradier, 2001 (N = 66)*
Age (y)	39.9±15	41 (9 – 72)	-
Weight (kg)	69.5±18.6	-	-
Africans-Caribbeans-W. Indies	25.6%	35%	-
Women	73.5%	82%	-
Fever	32%	-	50%
CNS involvement	53%	50%	90%
Autoimmunity	20%	-	13%
Hemoglobin (g/dL)	8 ± 2.2	-	7.2 ± 1.5
LDH (U/L)	6.2 ± 4.5	~ 5.5	-
Platelets (x10^9/L)	20.4 ± 19.2	11 (2 – 101)	35 ± 27
Creatinine (µmol/L)	127 ± 106	141 (61 – 581)	162 ± 140
ANA	53%	-	-
ESRD	0	-	1

Veyradier et al., Blood 2001; Coppo et al., Plos One 2010; Kremer Hovinga et al., Blood 2010; Mirouse et al., Crit Care Med 2021

Predictive features of severe ADAMTS13 deficiency

TABLE 1 PLASMIC score or French score predicts the likelihood of severe ADAMTS13 deficiency in a suspected TTP

Parameters	French Score	PLASMIC Score
Platelet count	<30 × 10^9/L (+1)	<30 × 10^9/L (+1)
Serum creatinine level	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis		
Indirect bilirubin >2 mg/dL	[a]	+1
or reticulocyte count >2.5%		
or undetectable haptoglobin		
No active cancer in previous year	[a]	+1
No history of solid organ or SCT	[a]	+1
INR < 1.5	[a]	+1
MCV < 90 fL	NA	+1
Likelihood of severe deficiency of ADAMTS13 activity (<10%)	0: 2%	0-4: 0%-4%
	1: 70%	6: 5%-24%
	2: 94%	6-7: 62%-82%

Platelet count < 30
+ Creatinine level <2.26
with no associated condition:

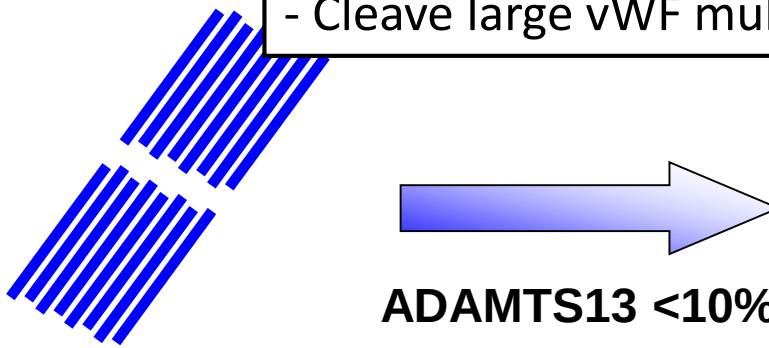
Surrogate markers consistently associated with ADAMTS13 <10%

ISTH guidelines for the diagnosis of TTP, J Thromb Haemost 2020

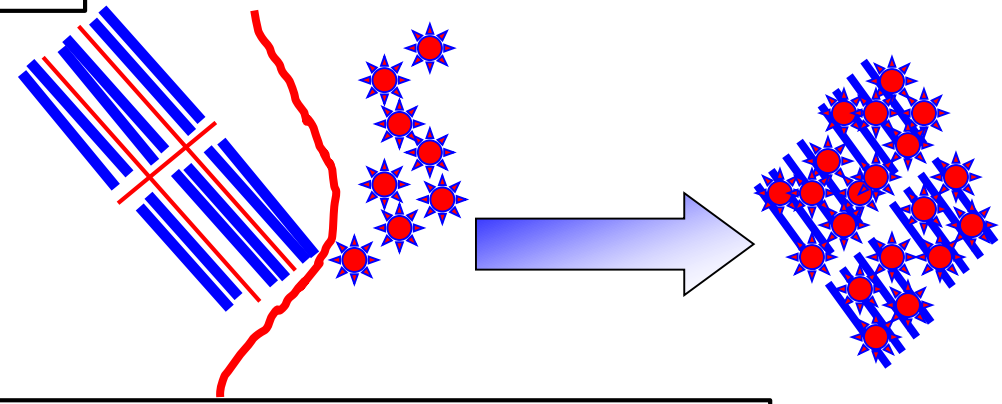
Pathophysiological basis of TTP treatment

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

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

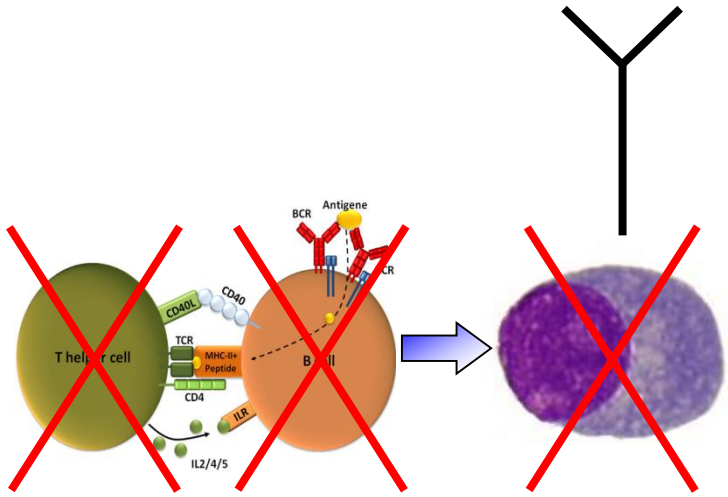


ADAMTS13 <10%



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

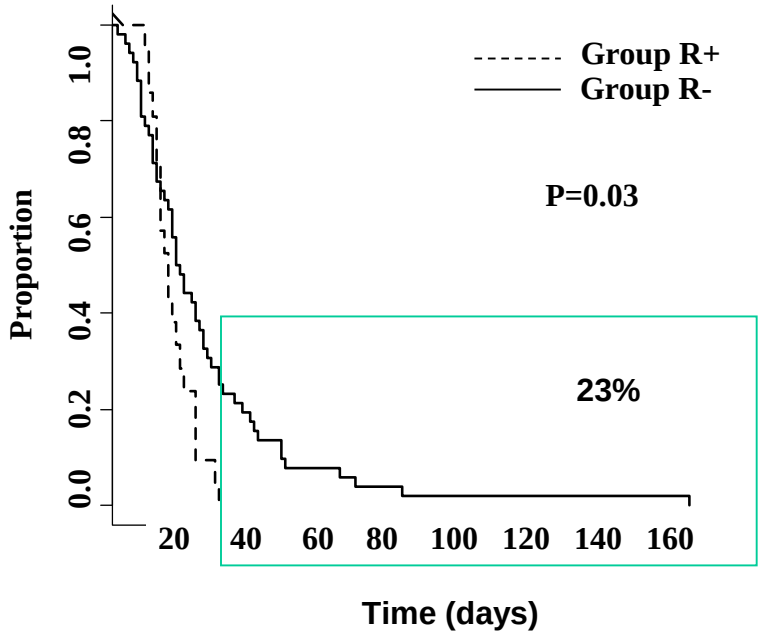
With this regimen, prognosis was outstandingly improved

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

Rituximab in acute iTTP to hasten recovery

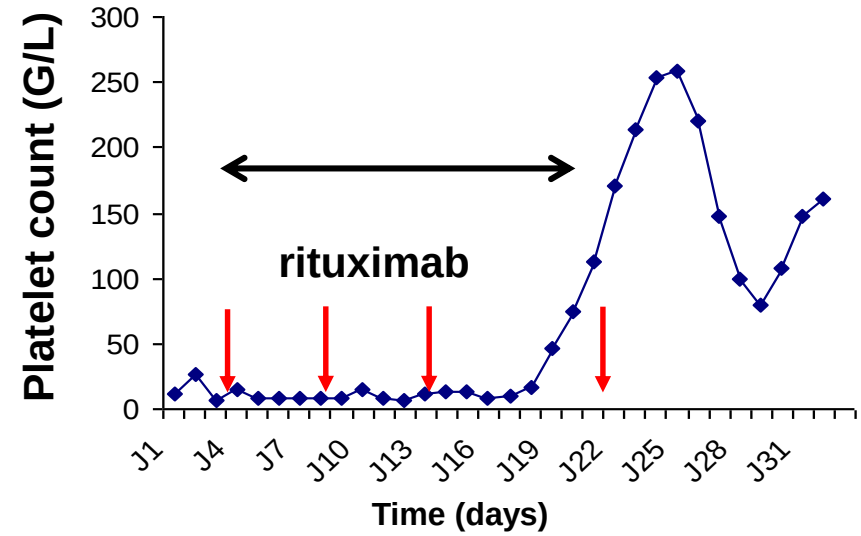
First as a salvage therapy, then frontline…

Rituximab prevents slow responses to TPE



Rituximab limits the duration of TPE treatment

Rituximab is not efficient in real time



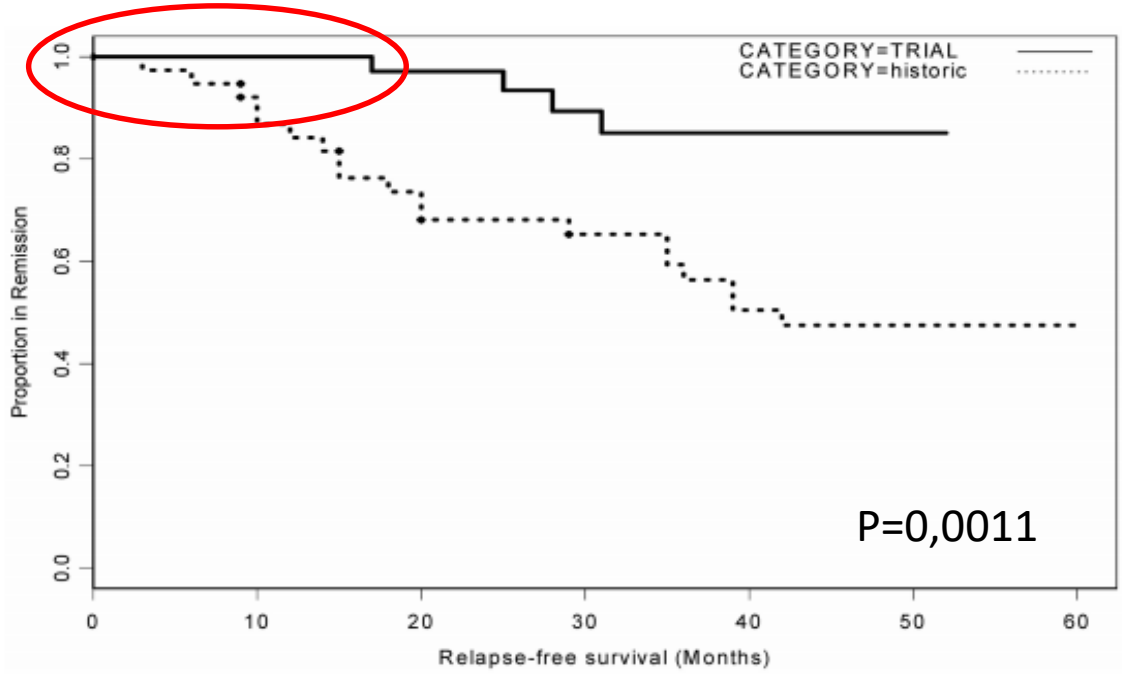
Mean time to platelet count recovery after the first rituximab infusion: 12 ± 6.7 d

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

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

Scully et al., Blood 2011

Patients are remarkably protected from relapses for 12-18 months

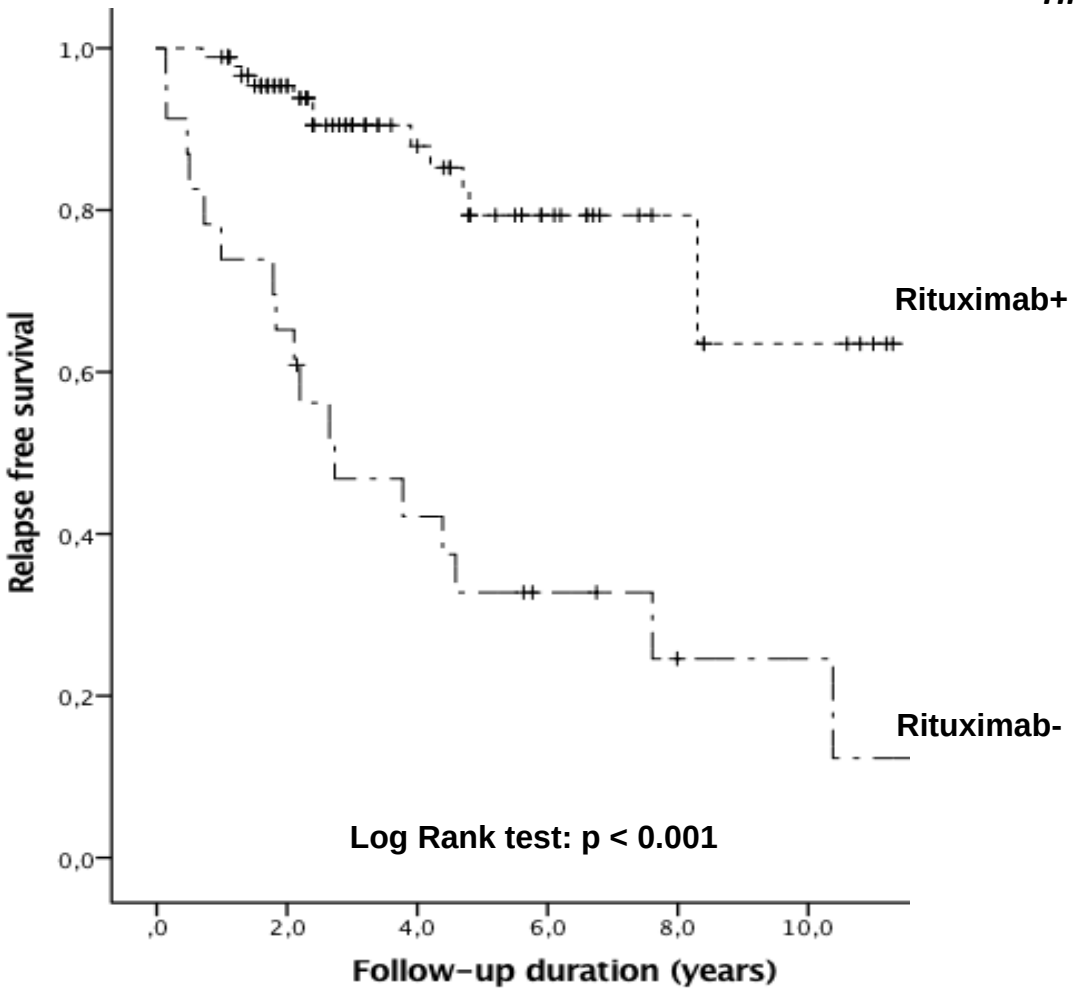


40% of patients w/o RTX remain with an undetectable (<10%) ADAMTS13 activity after the acute phase, and

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

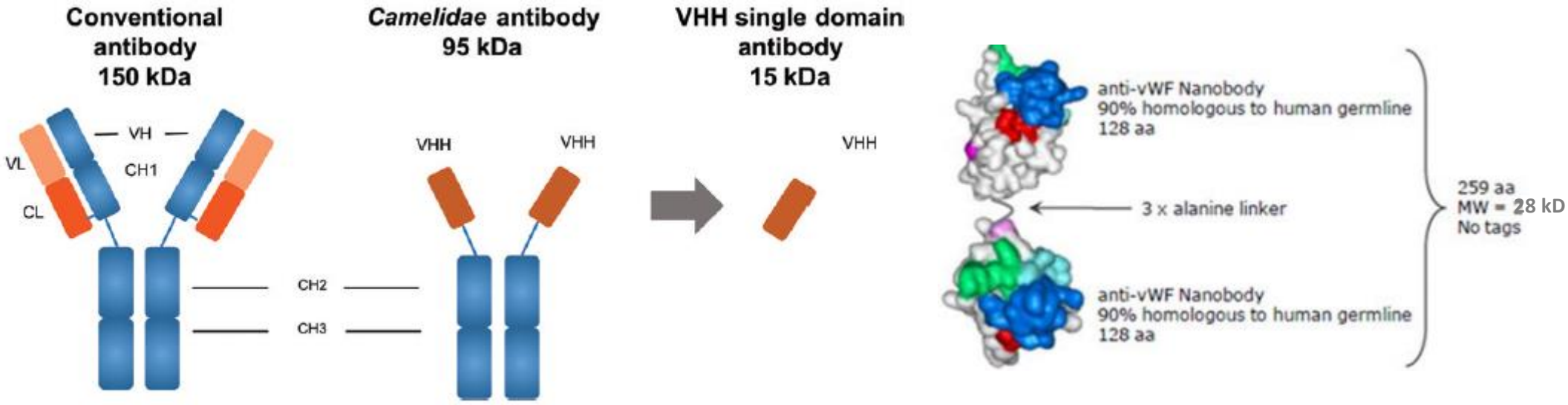
Rituximab: the guardian angel of ADAMTS13

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

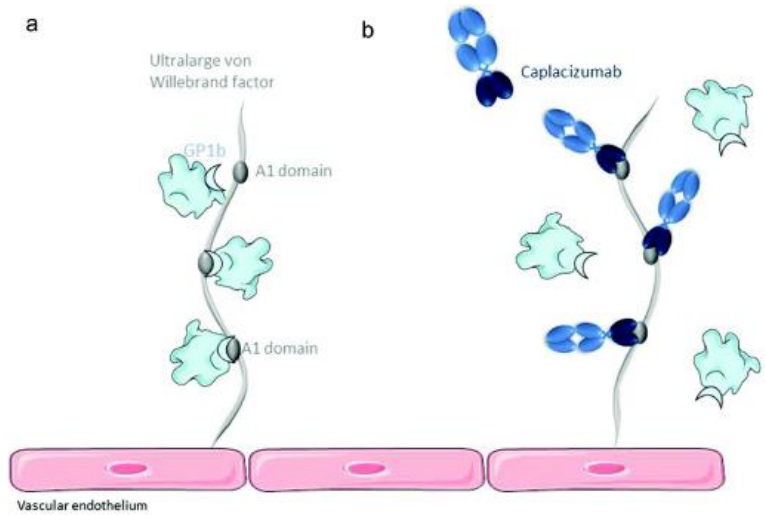


- Without preemptive treatment: 17/23 clinical relapses (74%) (multiple in 11) after a median follow-up of 7 y;
- Cumulative incidence of relapse: 0.26/y

Caplacizumab: a small antibody with big implications for iTTP



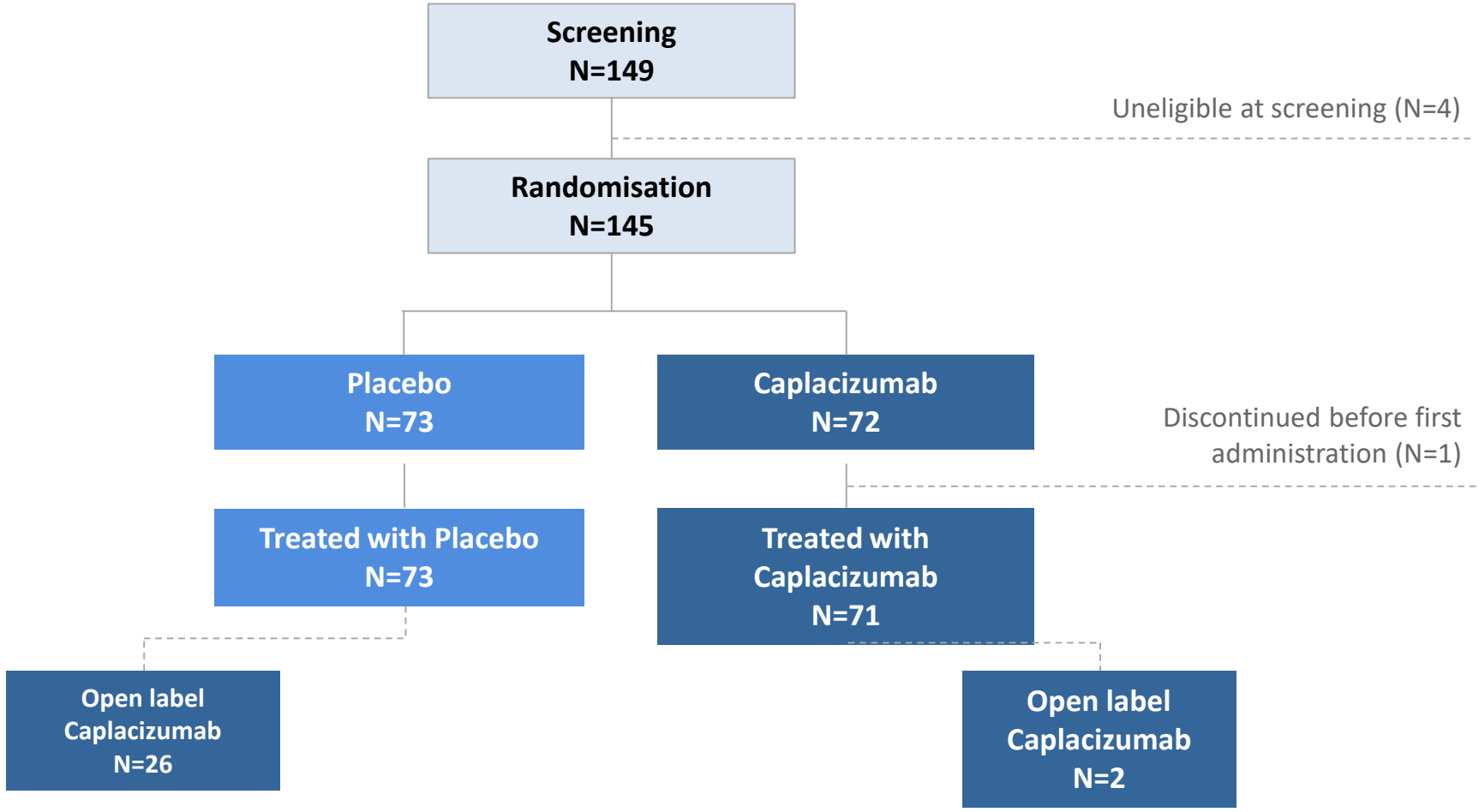
Therapeutic class of proteins derived from the heavy-chain variable domains that occur naturally in heavy-chain Ig from *Camelidae*



Poullin et al., Drugs of Today, 2019

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

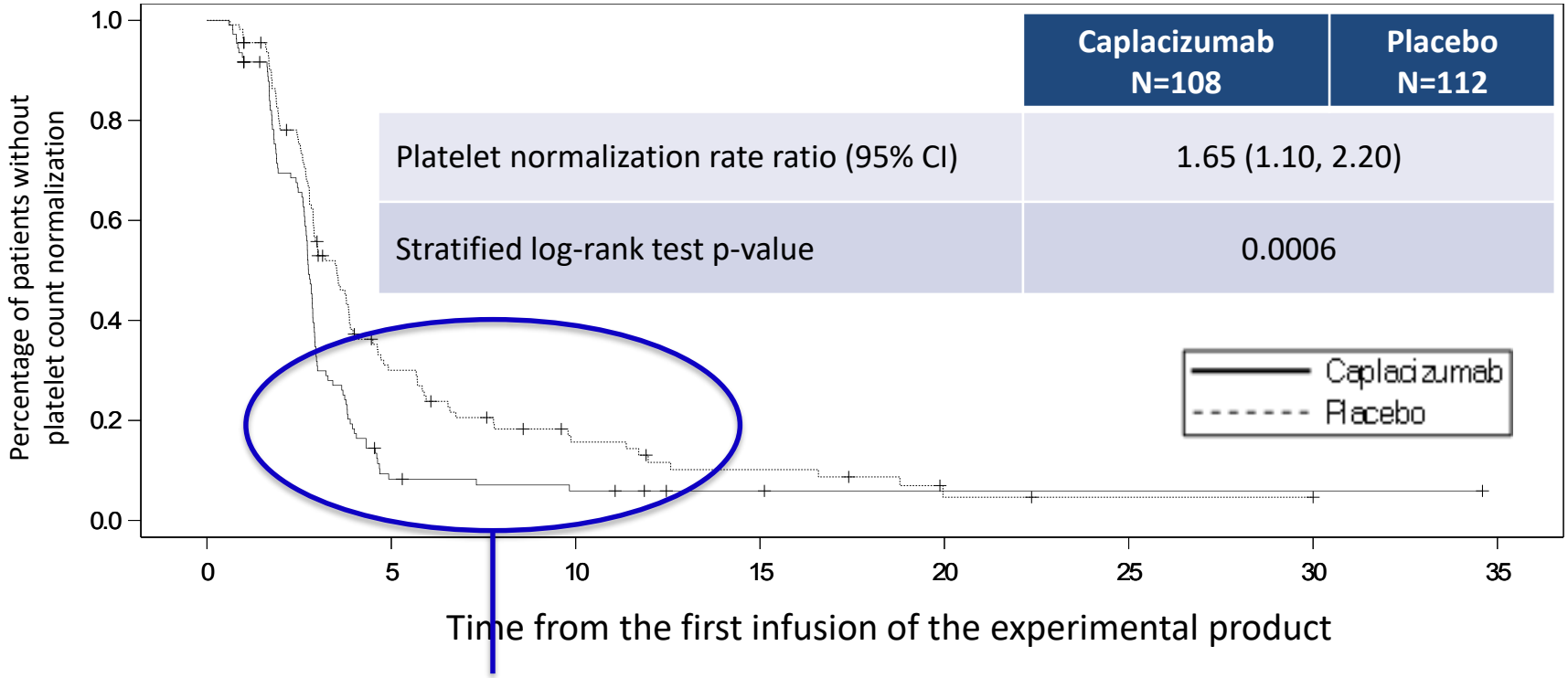
Flow chart (HERCULES):



Scully, Cataland, Peyvandi, Coppo et al., N Engl J Med 2019; Peyvendi, Cataland, Scully, Coppo et al. Blood adv. 2021

Primary endpoint: time to first platelet count recovery

Integrated analysis (TITAN + HERCULES):



Rituximab inefficient

Caplacizumab makes a bridge until rituximab efficacy

Peyvandi et al. Blood adv. 2021

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

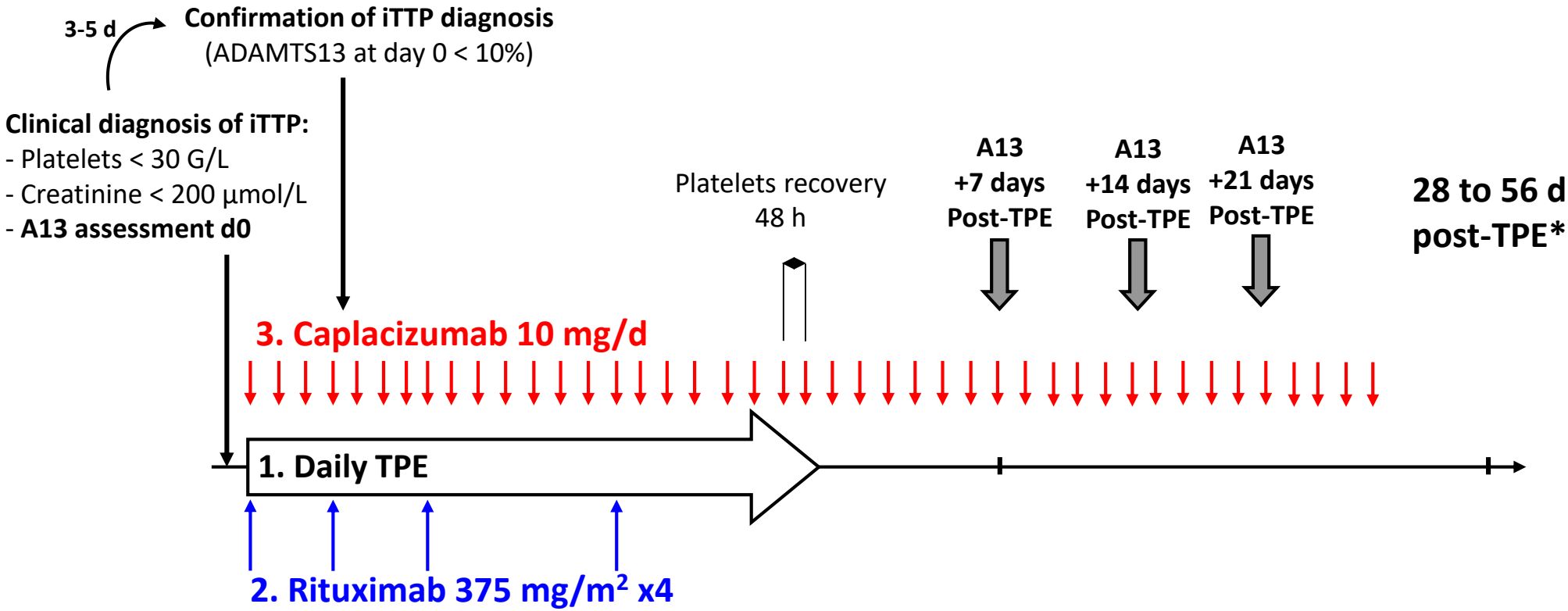
Peyvandi et al. Blood adv. 2021

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

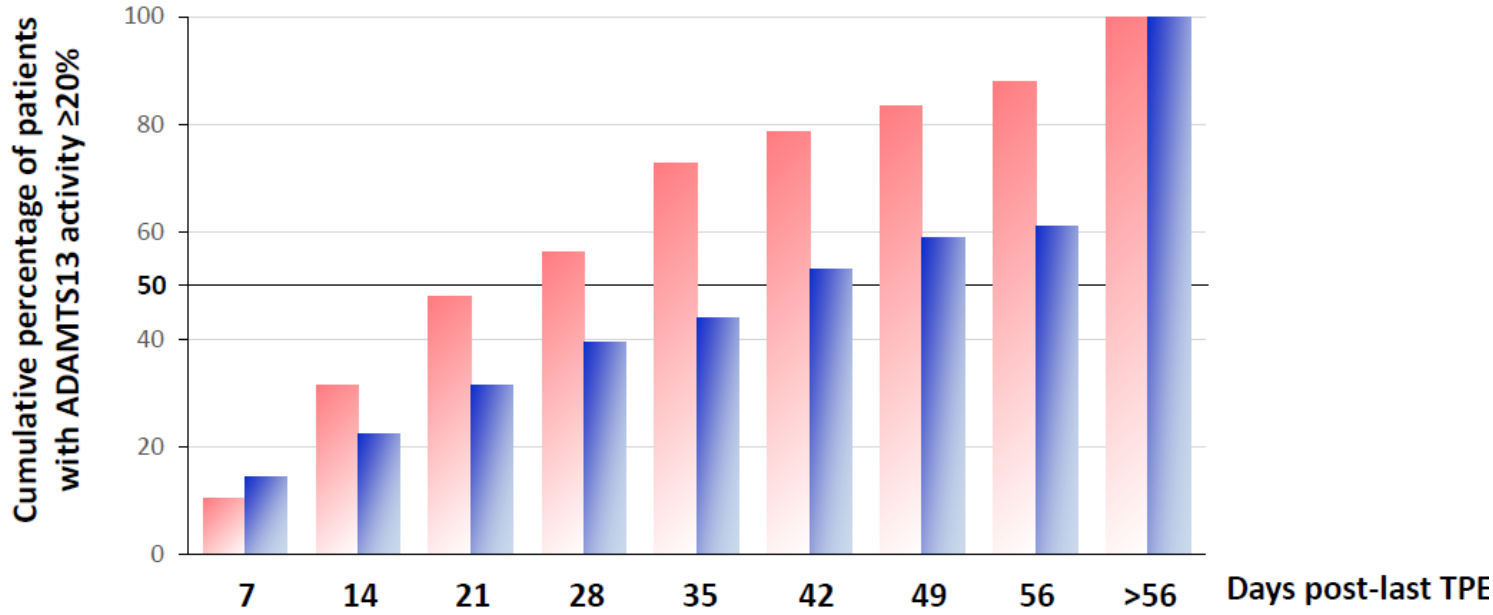
Better prognosis

↓ 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, Benhamou 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, Benhamou et al., Blood 2021

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,

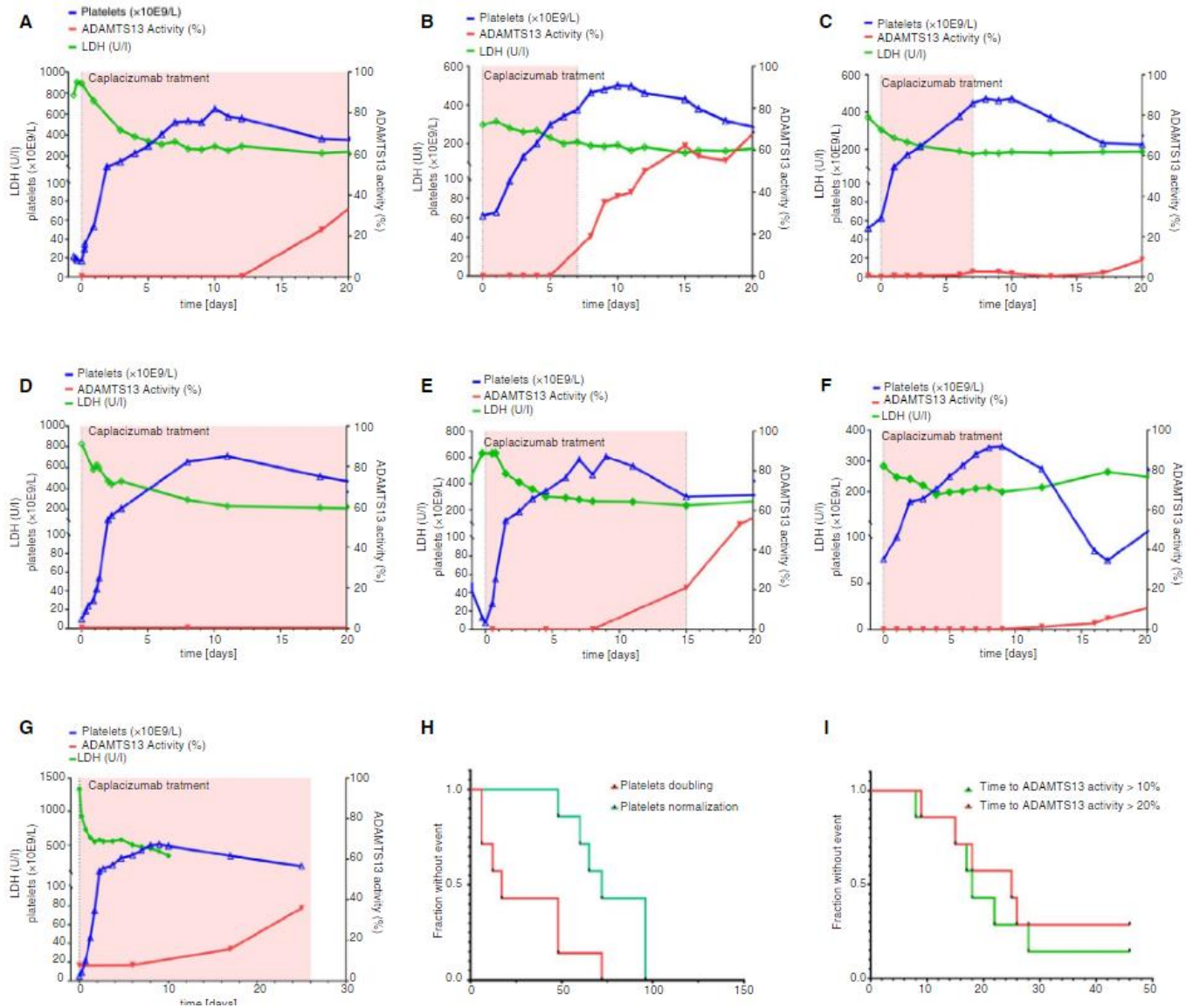
Abstract

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?

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

Why patients with TTP still die…?

Mrs F… D…, 45 yo

Feb, 15th 2007, in the evening : nauseas + epigastric pain following a meal of mussels the day before

Feb, 16th: vomiting and hematemesis + jaundice => GP

Feb, 17th in the morning: abdominal ultrasound sonography normal + blood cell count: platelets 6 G/L + Hb 9.6 g/dL

Feb, 17th in the evening: hospitalized in emergency (referred by her GP)

Feb, 18th 4.00 am: schistocytes+++ = treatment by steroids alone for « ITP »

Feb, 18th 8.50 am : sudden death by cardiorespiratory arrest

Diagnosis of iTTP made post-mortem; ADAMTS13 on an aliquot of serum <10%...

Mrs D… S…, 44 yo

Hospitalized in <u>July, 2021</u> for hemorrhage with bicytopenia

Past medical history:

- Hashimoto's thyroiditis

- Hypothyroiditis + vitamin B12 deficiency in the sister

History:

- Blood cell count and serum creatinine normal on August, 2020

- July, 10th 2021: « black » urines withhematuria; an episode of chills, with lumbar pain

- July, 11th : consults to emergency room:

  Hemoglobin 10,4 g/dL, platelets 23 G/L, MCV 89 fl, reticulocytes 109 G/L, haptoglobin decreased, total bilirubin 27 µmol/L, LDH 1.5N, DAT negative, schistocytes 1% then 2%, serum creatinine 78 µmol/L

  Treatment: corticosteroids 1 mg/kg/d + C3G +vitaminotherapy B12 ; suspicion of pernicious anemia

- July, 13th: transfered to a medical department

  Bone marrow aspiration hypercellular, many megakaryocytes consistent with a peripheral thrombocytopenia

Diagnostic hypotheses raised:

- Pernicious anemia (familial context, folates and vitamin B12 low)
- TMA (TTP or HUS) (but no renal failure or CNS involvement) (ADAMTS13 sampled on July, 15th)
- Autoimmune thrombocytopenia
- Autoimmune cytopenias associated with a lymphoproliferative disease
- Acute leukemia

Treatment:

Prednisone pursued 1 mg/kg/d + oral vitamin B12

Outcome:

- July, 16th, 6 am: conscient, orientated with no complain according to the nurse

  at 9 am: unconscious (Glasgow 8), agitated, mydriasis, AP very low.
  Transfusion of RBC + platelets
  Transferred to ICU; diagnosis of TTP made; intubated – Cerebral TDM : no hemorrhage (normal+++)
  11.40 am: bradycardia, electro-mecanic dissociation and death

iTTP (ADAMTS13 <5%)

Learning by experience can be painful…

…but it is still more painful not to learn from experience…

To make clinicians aware of TTP diagnosis remains one of the most important issues

It is likely that a substantial number of TTP patients still die before diagnosis…

Grall et al., Am J Hematol 2017; Joly et al., Lancet Haematol 2017

Misdiagnosis in iTTP

84/423 patients (20%) have initially a wrong diagnosis

	Alternative Dg	Dg TTP
Neurologic involvement	63% (53)	70% (241)
Headache	27% (23)	28% (61)
Confusion	19% (16)	19% (65)
Seizure	12% (10)	9% (33)
Coma	27% (23)	19% (65)
Focal deficiency	34% (29)	38% (129)
Cardiac involvement	33% (28)	30% (102)
Organ involvement before TTP diagnosis	**67% (56)**	**80% (273)**

Alternative diagnosis, despite frequent organ involvement

TABLE 2 Association between patients' characteristics and diagnostic error by multivariable analysis

Parameters	Odds ratio	95% CI	*P* value
Sex (female)	2.33	1.12–5.12	0.02
AID on diagnosis	1.56	0.73–3.34	0.25
Hemoglobin level (per unit increased)	1.20	1.02–1.43	0.03
Positive DAT	6.88	1.84–33.82	0.004
Low or undetectable schistocytes	3.17	1.73–5.93	<0.001
Positive ANA	1.68	0.89–3.23	0.11

ANA = antinuclear antibodies, AID = autoimmune disorder, DAT = direct antiglobulin test, CI = confidence interval. A *P* value < 0.05 was considered to be statistically significant. Significant values appear in bold.

DAT may be positive… and schistocytes rare

Time from hospitalization to TTP diagnosis = 5 d (alternative diagnosis) vs 1 d (Dg TTP)

Grall et al., Am J Hematol 2017

Diagnosis of TTP: a « pentade »

- Cerebral involvement

- Renal failure

- Fever

- MAHA

- Thrombocytopenia

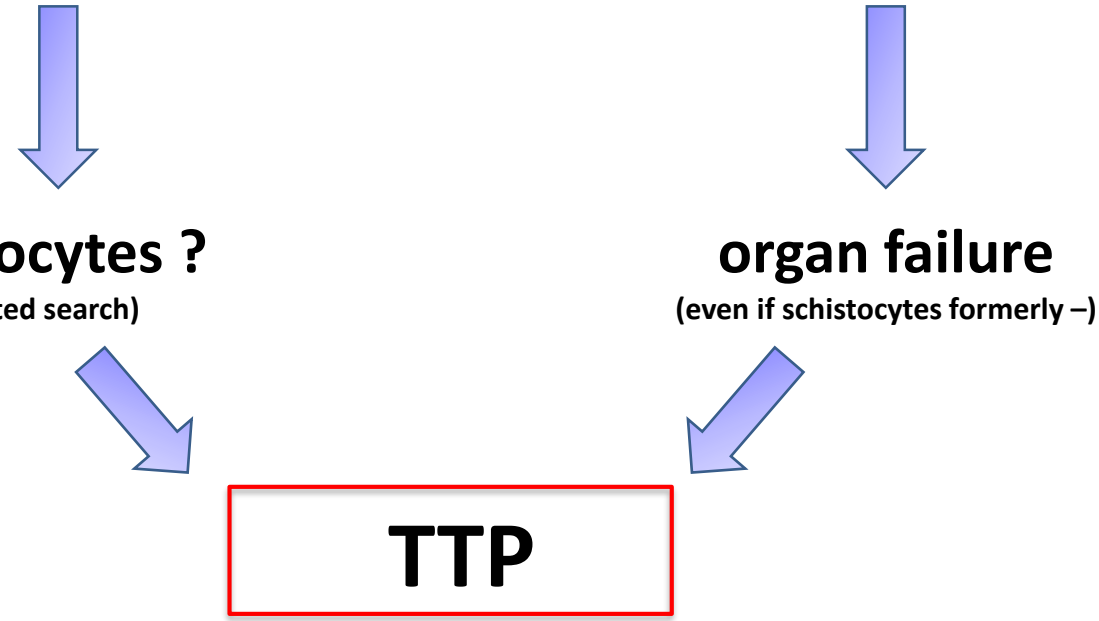
An early diagnosis is mandatory+++

Late diagnosis, pre-mortem……..

Amorosi & Ultmann, Medicine 1966

What you need to know to save a patient with iTTP

1. Thrombocytopenia + hemolytic anemia/hemolysis



2. Refer the patient to/contact a trained team for treatment immediately

https://www.cnr-mat.fr/

Clinical case

A 46-yo woman is admitted to the emergency room for purpura, bruises, and a transient weakness of left arm.
She has a past history of overweight and autoimmune thyroiditis. She originates from West Indies.
Neurological examination is unremarkable at admission.

Hemoglobin	9 g/dL
Platelet count	7 K/L
Reticulocytes	135 K/L
LDH level	2xN
Unconjugated bilirubin	1.5xN
Haptoglobin	< normal
Serum creatinine	150 µmol/L (1.7 mg/dL)
B-HCG	Negative
HIV	Negative

ADAMTS13 activity and anti-ADAMTS13 antibodies were sampled and will be available within 5 days.

Which of the following items are correct?

1. The French score of this patient is consistent with a TTP

2. The French score of this patient is consistent with an HUS

3. This patient should receive daily PEX + corticosteroids from day-1

4. This patients should receive daily PEX + corticosteroids / rituximab + caplacizumab from day-1

5. Caplacizumab should be started after ADAMTS13 activity confirms TTP diagnosis

Which of the following items are correct?

1. The French score of this patient is consistent with a TTP (score = 2)

2. The French score of this patient is consistent with an HUS

3. This patient should receive daily PEX + corticosteroids from day-1

4. This patients should receive daily PEX + corticosteroids / rituximab + caplacizumab from day-1

5. Caplacizumab should be started after ADAMTS13 activity confirms TTP diagnosis

Zheng et al., ISTH recommendations; J Thromb Haemost 2020; Eller et al., Nephrol Dial Transplant 2022

Conclusion: Towards more precision medicine to improve iTTP prognosis

1. With current highly active treatments, most patients survive from the acute phase of iTTP; however, deaths still occur as a result of diagnostic delay

2. To make clinicians more aware of TTP diagnosis is a major goal to improve the prognosis of the disease

3. Targeted therapies based on anti-vWF agents (caplacizumab) and rADAMTS13, that are efficient immediately, nicely prevent unfavorable outcomes in iTTP; next steps: to monitor ADAMTS13 activity to personalize caplacizumab regimen; PEX-free regimens

4. With those new highly efficient therapeutic regimens, the only limitating factor to improve early prognosis in TTP is the time to diagnosis

To fight against diagnostic delay is now the most crucial issue in TTP

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