Present and future of TTP treatment

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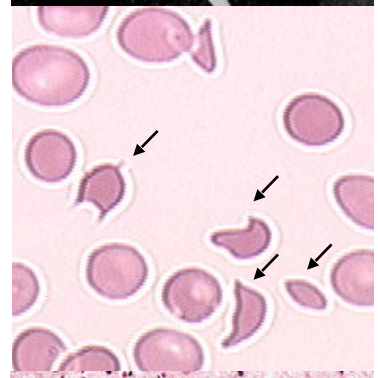
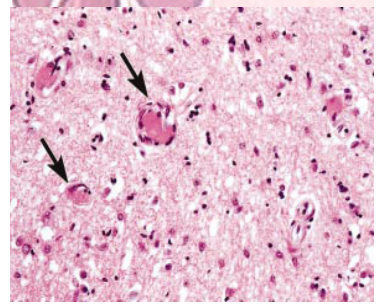
CNR-MAT EuroBloodNet webinar on TMAs - 2021

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

Associated condition

Idiopathic

2-3 cases / 10^6 hab /y

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

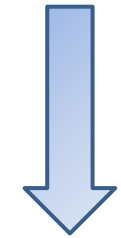
Veyradier et al., Blood 2001; Coppo et al., Plos One 2010; Kremer Hovinga et al., Blood 2010

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:



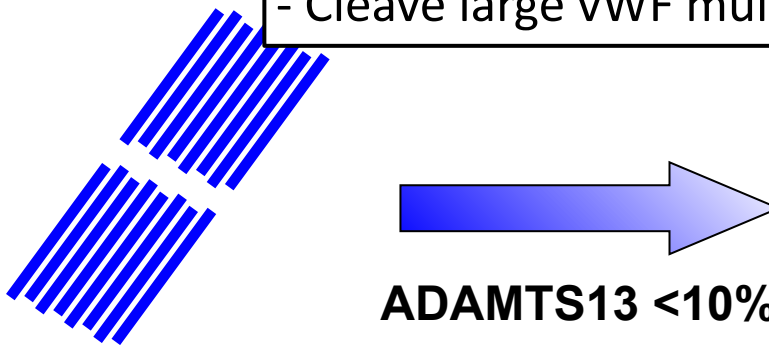
consistently associated with severe ADAMTS13 deficiency

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

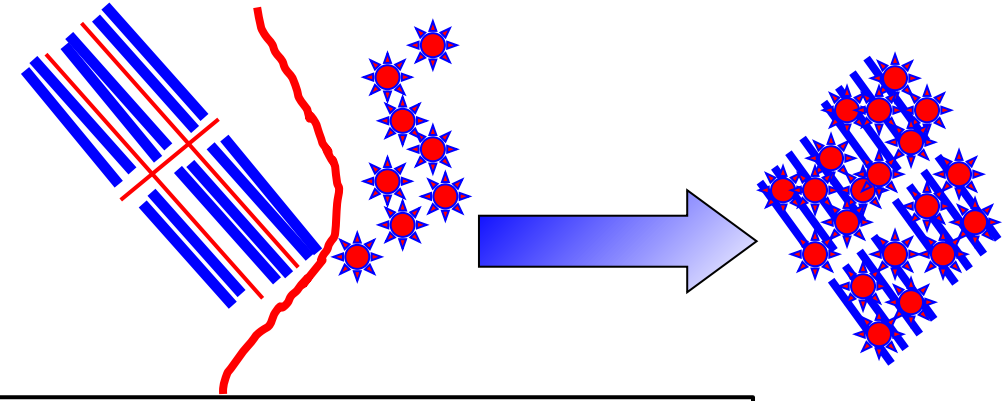
Pathophysiological basis of iTTP treatment

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

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

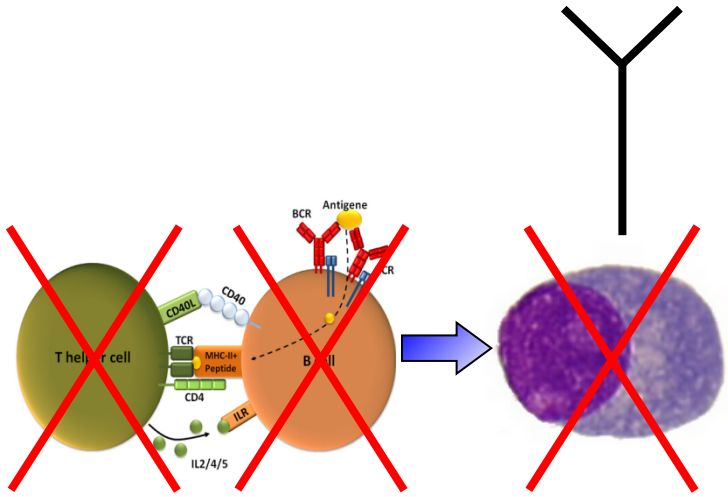


ADAMTS13 <10%



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

Standard 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.

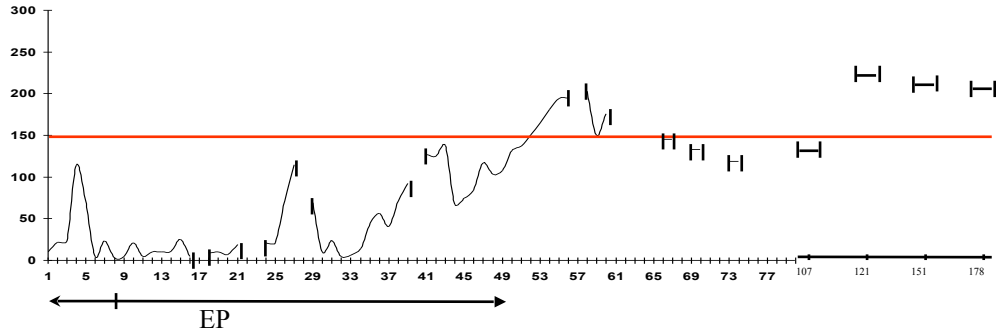
Daily therapeutic plasma exchange + steroids in emergency until remission = core treatment of TTP

With this regimen, prognosis was outstandingly improved

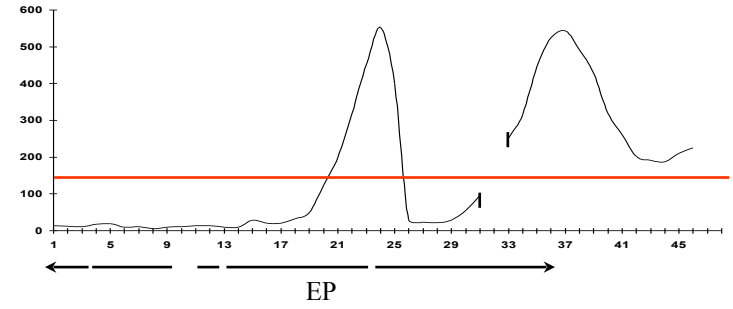
Remission/survival is currently of 85%, vs almost 0% before

Unmet needs with standard treatment

Exacerbations (~ 50% of patients)



Refractoriness (~ 10% of patients)



Patients with a <u>suboptimal response</u> to standard treatment

Exposed to a higher risk of death

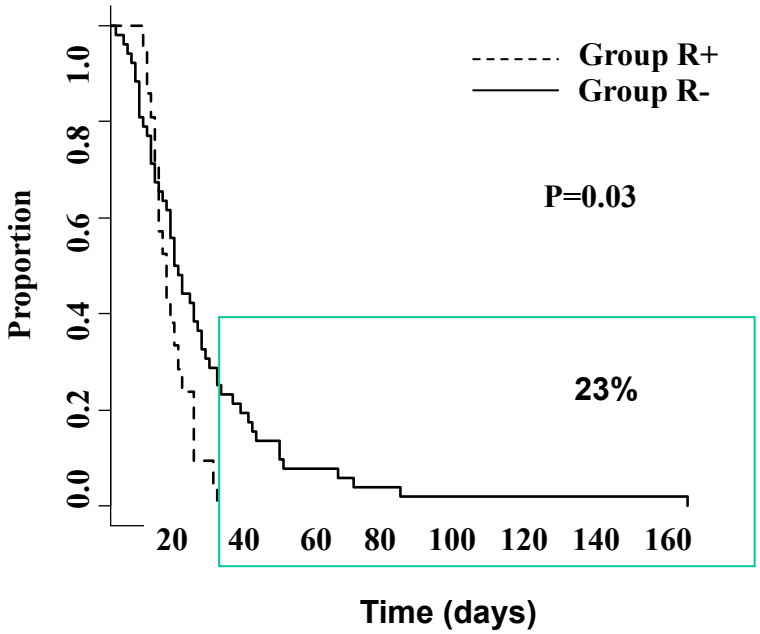
TPE-related complications (28% of cases)

How to improve these results?

CNR-MAT, Br J Haematol 2006; Howard et al., Transfusion 2006

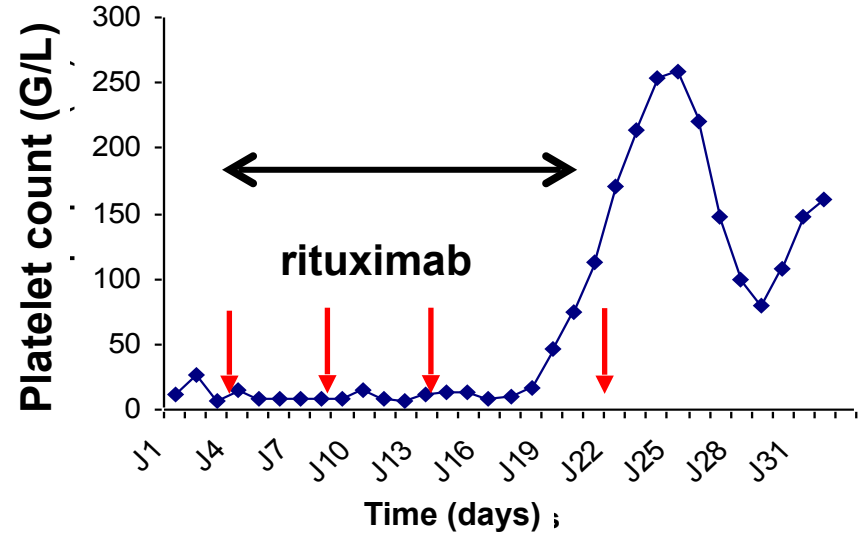
Rituximab in acute iTTP with suboptimal response

Rituximab prevents long term 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

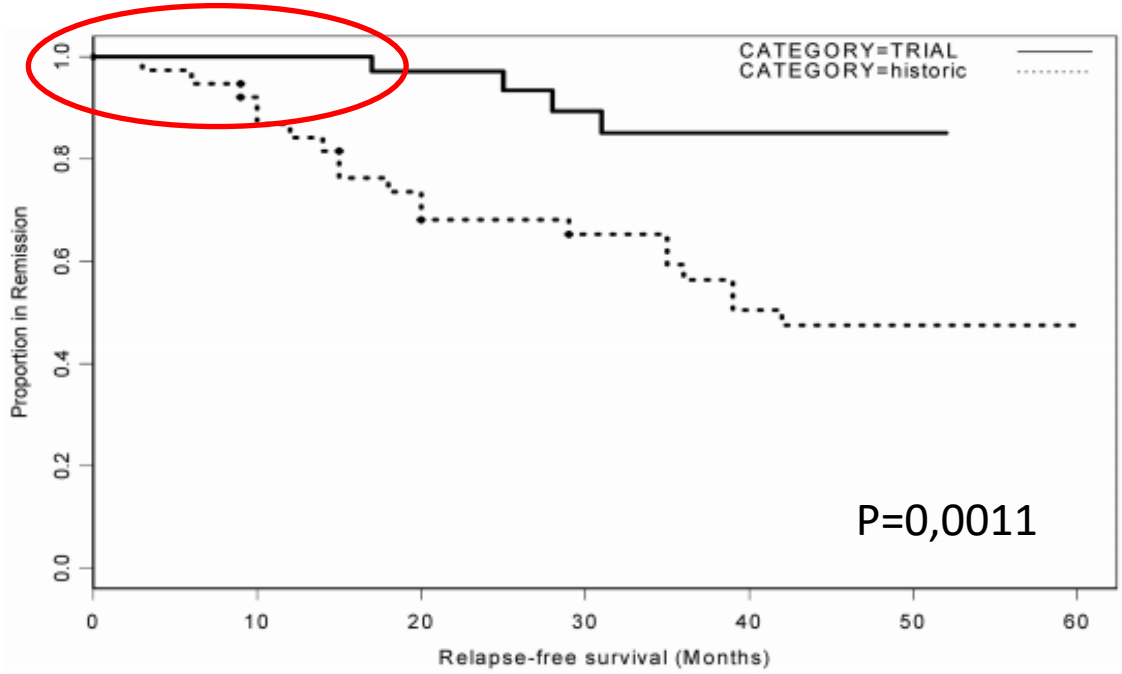
Scully et al., Br J Haematol 2007; CNR-MAT, Crit Care Med 2012

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

Should all patients receive rituximab front-line???

Scully et al., Blood 2011

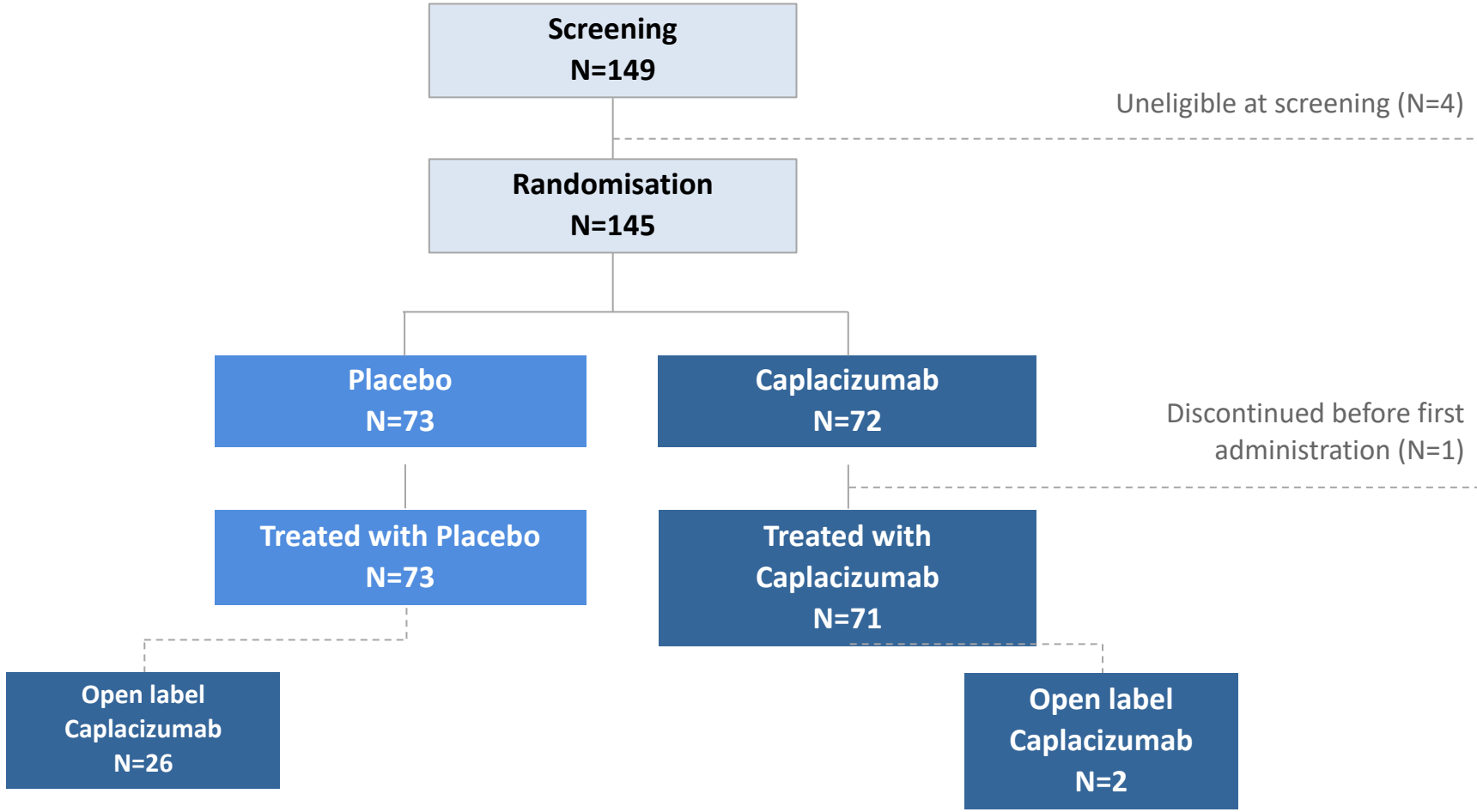
Risk of overtreatment for a significant nb of patients at the acute phase….. but patients are remarkably protected from relapses for 12-18 months



40% of patients remain with an undetectable (<10%) ADAMTS13 activity after the acute phase, and 40% others remain with a decreased (10-50%) activity

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

Flow chart (HERCULES):

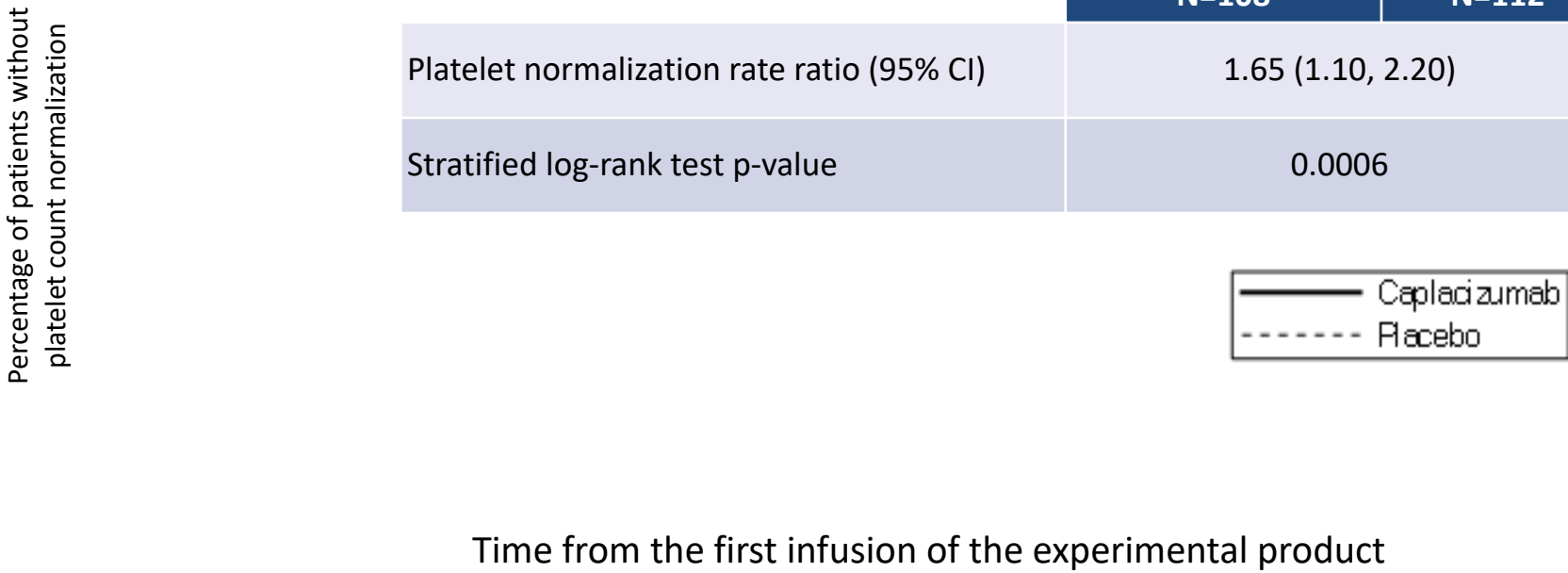


Scully, Cataland, Peyvandi, Coppo et al., N Engl J Med 2019

Primary endpoint: time to first platelet count recovery

Integrated analysis (TITAN + HERCULES):

	Caplacizumab N=108	Placebo N=112
Platelet normalization rate ratio (95% CI)	1.65 (1.10, 2.20)	
Stratified log-rank test p-value	0.0006	



Less exposure to thrombocytopenia = less exposure to death

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

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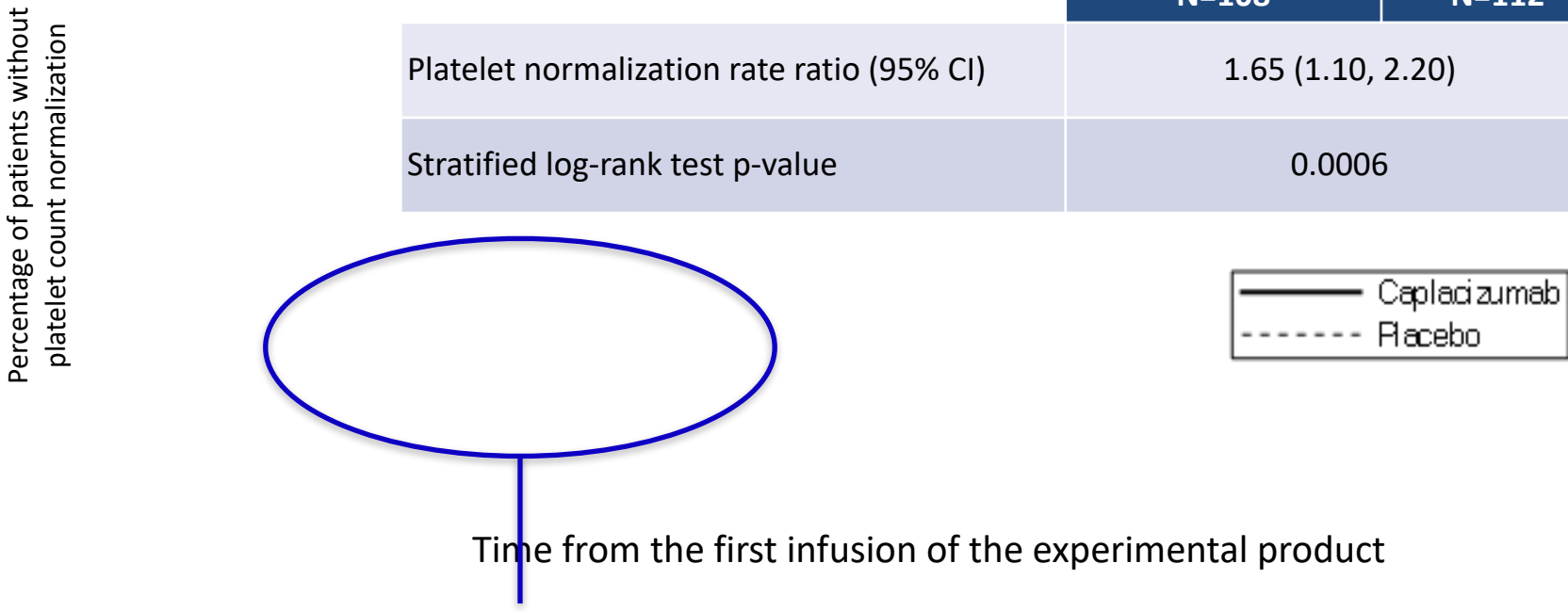


Caplacizumab makes a bridge until rituximab efficacy

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

Composite criteria – Death, recurrences and major TEE

TITAN + HERCULES	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**	

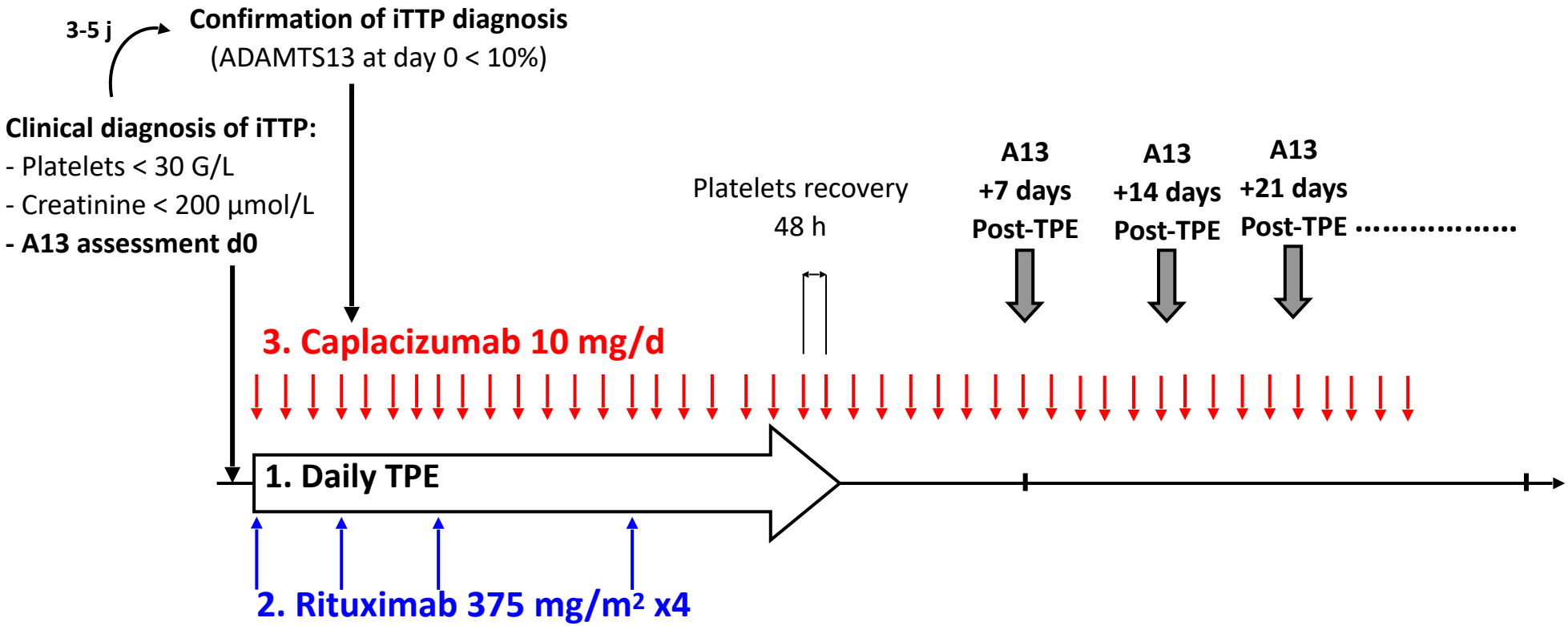
Mortality/refractoriness during treatment	Caplacizumab N=108	Placebo N=112
Mortality – n (%)	**0**	**4 (3.6)**
95% CI	NA	(1.0, 8.9)
p-value	**0.0477**	
Refractoriness – n (%)	**0 (0.0)**	**7 (6.3)**
95% CI	NA	(2.5, 12.5)
p-value	**0.0089**	

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

Caplacizumab after the Greec epic: where do we stand?

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

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



Clinical Features and Concomitant Treatment

Characteristic	Triplet regimen (N = 90)	Historical cohort (N = 180)	*P* - value
Age (years)	45 (34–57)	43 (30–57)	1.00
Women, n (%)	63 (70%)	127 (70%)	0.30
Body mass index (kg/m^2)	27.2 (22.7–32.2)	26.6 (23–31.7)	0.68
Ethnicity, n White African-West Indies Asian	 74 10 6	 149 25 6	0.39
Ongoing platelet agent/anticoagulation, n (%) Antiplatelet agent Anticoagulant	9 (10%) 7 2	16 (8.9%) 11 5	0.77
Relapse, n (%)	12 (13.3%)	21 (11.7%)	0.70
Cerebral involvement, n (%) Headache Confusion Seizure Coma Focal deficiency	55 (61%) 19 22 10 2 20	111 (62%) 58 36 15 5 26	0.91
Cardiac involvement, n (%)	51 (56%)	86 (47%)	0.15

Data provided as medians (IQR) for continuous values and number/total number of patients (%) for qualitative values

Coppo et al., Blood 2020

Clinical Features and Concomitant Treatment

Characteristic	Triplet regimen (N = 90)	Historical cohort (N = 180)	*P* - value
Hemoglobin (g/dL)	8.9 (7.5–10.2)	8.6 (7.3–10.1)	0.54
Platelet count (x 10^3/mm^3)	12 (10–20)	12 (8–23)	0.88
LDH level x normal (xN)	5.1 (4.0–6.5)	3.7 (2.4–5.6)	0.01
Serum creatinine level (µmol/L)	92 (71–120)	86 (68–133)	0.17
GFR (mL/min/1.73m^2) (MDRD)	74 (51–108)	80 (46–120)	0.85
Anti-ADAMTS13 antibodies (U/mL)	78 (39–91)	80 (36–100)	0.44
French Severity score 0–2 3–4	 72 (81%)[a] 17 (19%)	 145 (87%)[b] 21 (13%)	 0.37
Immunosupressive therapy Corticosteroids Rituximab Time between first infusion and first TPE	 88 (98%) 90 (100%) 2 (1–3)	 166 (92%) 123 (68%) 7 (4–10)	 0.10 <0.01 <0.01
Other therapies Twice-daily TPE Cyclophosphamide Splenectomy Vincristine Bortezomib >1 salvage therapy	0	25 (13.9%) 20 4 2 3 1 4	<0.01

These features are comparable to those of epidemiological studies

These patients are representative of iTTP population in real life

Good compliance from practitioners to the therapeutic regimen

Patients at high risk of early death of iTTP were defined by a French severity score ≥3 (cerebral involvement: yes=1 / no=0, LDH: >10xULN=1 / ≤10xULN=0, age: >60 y=2 / >40 and ≤60 y=1 / ≤40 y=0)[2]
Data provided as medians (IQR) for continuous values and number/total number of patients (%) for qualitative values.
[a]From 89 patients; [b]From 166 patients.

Coppo et al., Blood 2020

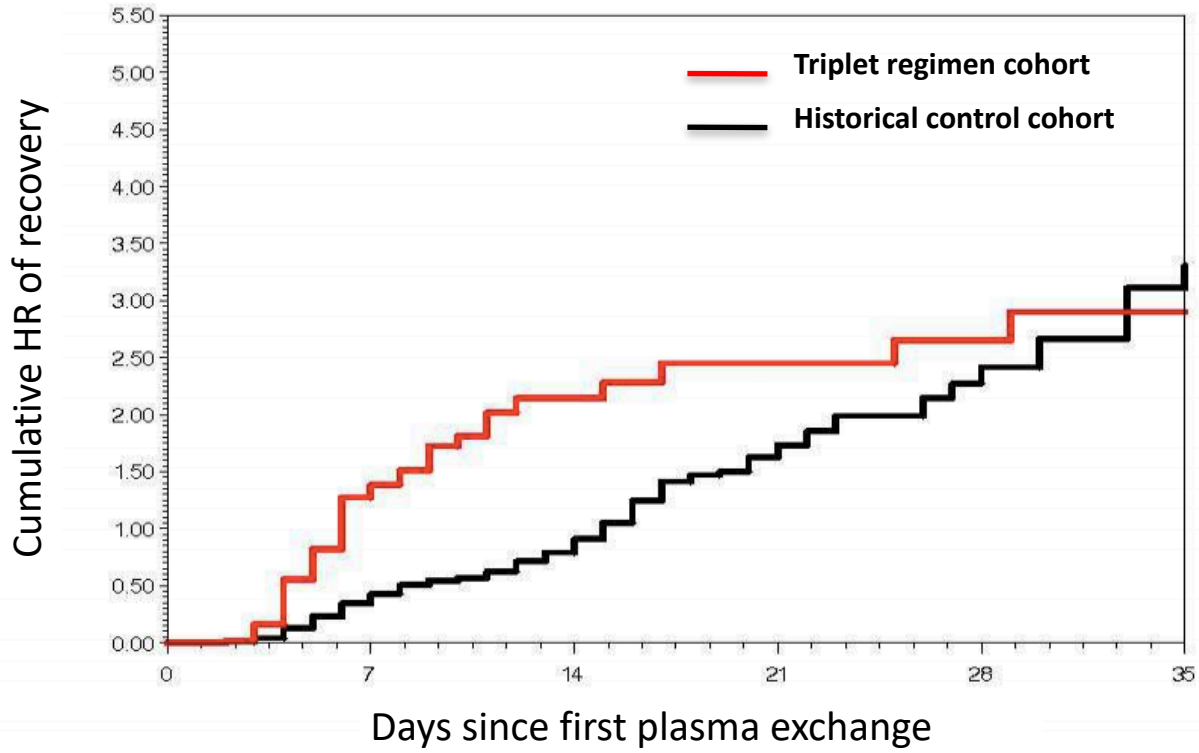
Primary and Secondary Outcomes According to the Treatment Regimen

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
Thromboembolic events	11 (12%)	20 (11.1%)	0.79

(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 2020

Cumulative HR for Platelet Count Recovery

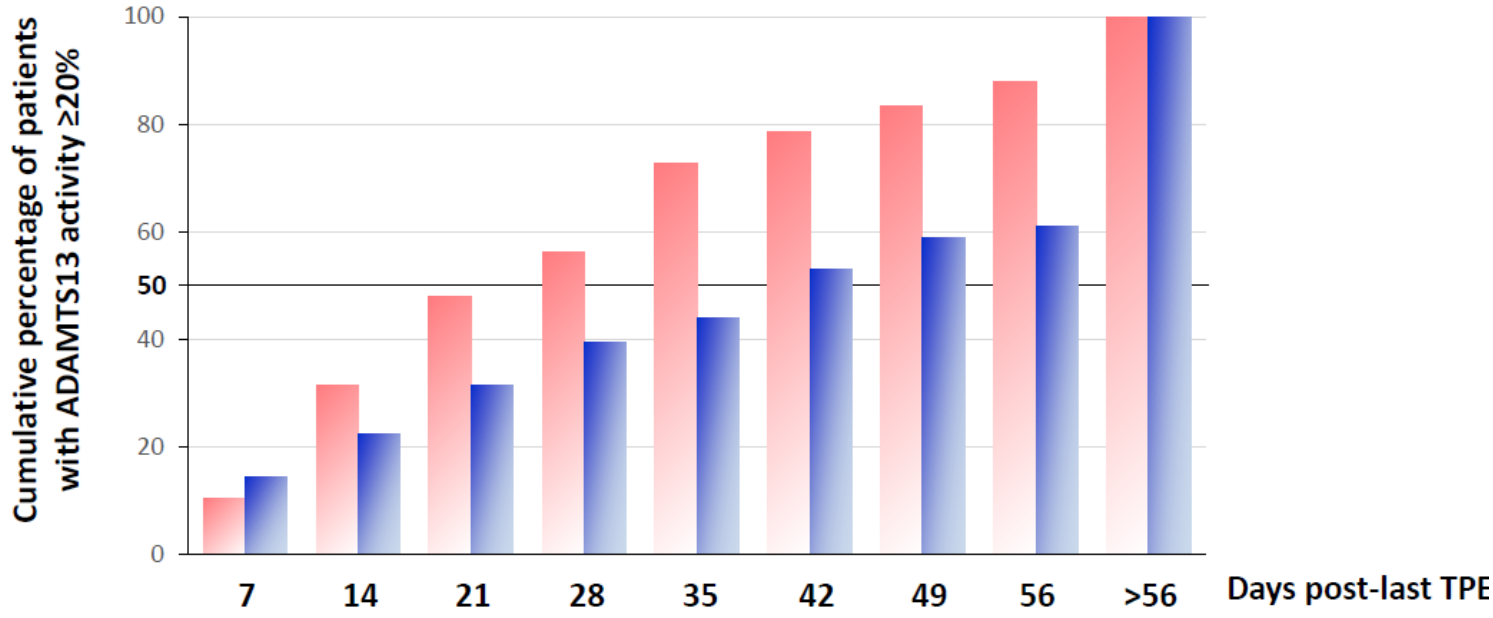


Patients in the triplet cohort recovered durable platelet count 1.8 more rapidly than those in the historical cohort (<0.01)

Time to durable platelet count is defined as time from first treatment to last daily TPE during the overall treatment period.
HR, hazard ratio; TPE, therapeutic plasma exchange.

Coppo et al., Blood 2020

Time to ADAMTS13 Improvement (> 20%)



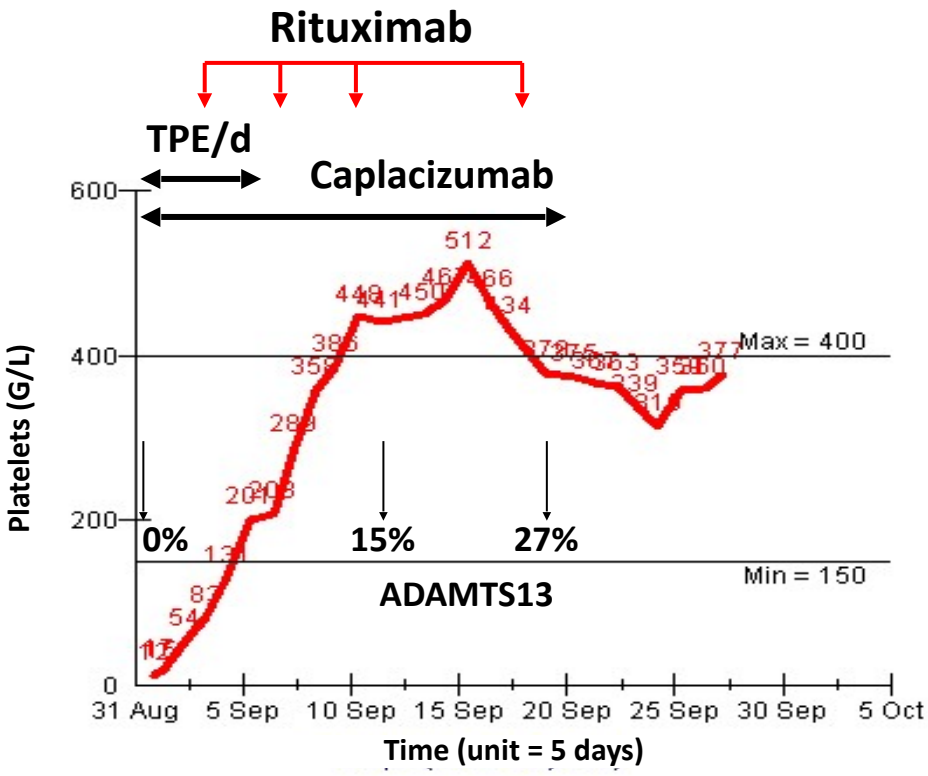
Triplet regimen cohort

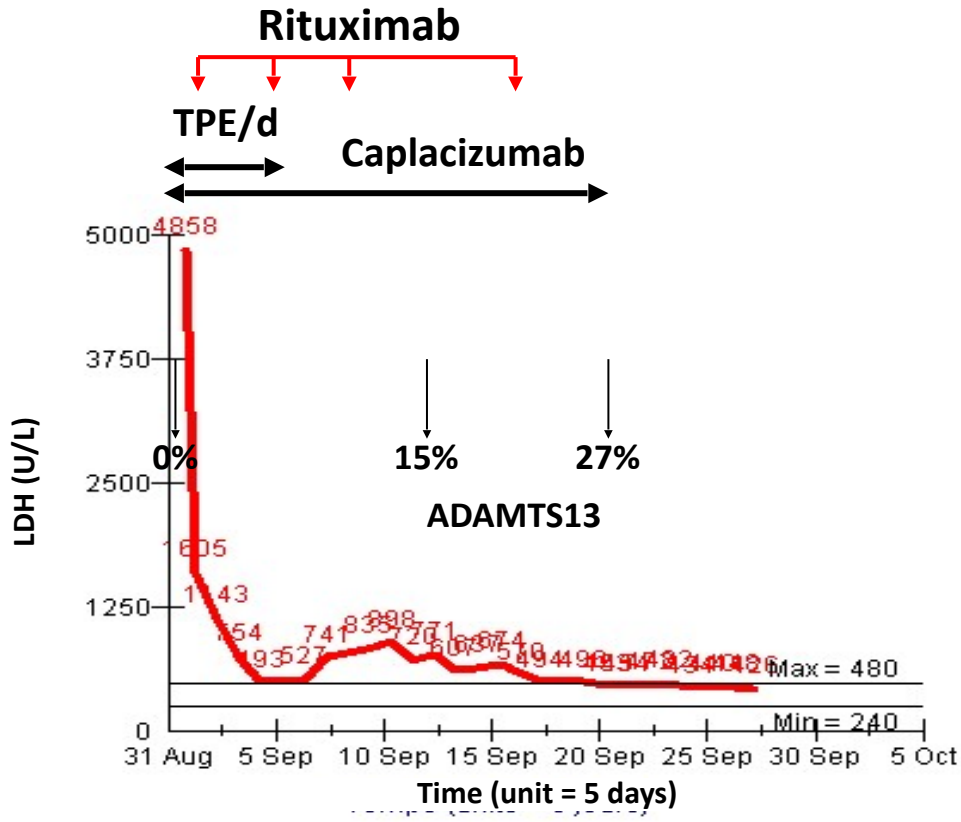
Historical treatment cohort

Coppo et al., Blood 2020

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%[b]

Caplacizumab could negativate the worse prognosis of cerebral and cardiac involvement

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 2020

Prevention of relapses

Concerns raised by relapses in TTP

- Relapse remains a severe condition
- The severity of a relapse is not predictable from the severity of previous episodes

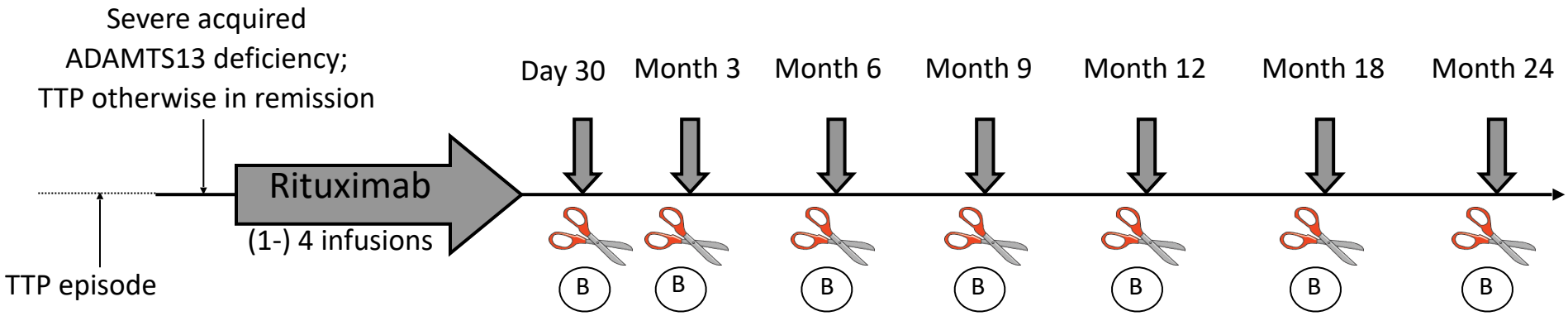
Relapse episodes:
- may have therapy-related complications
- may worsen depression and cognitive impairment

Patients can die from a relapse

Relapse prevention is a major goal

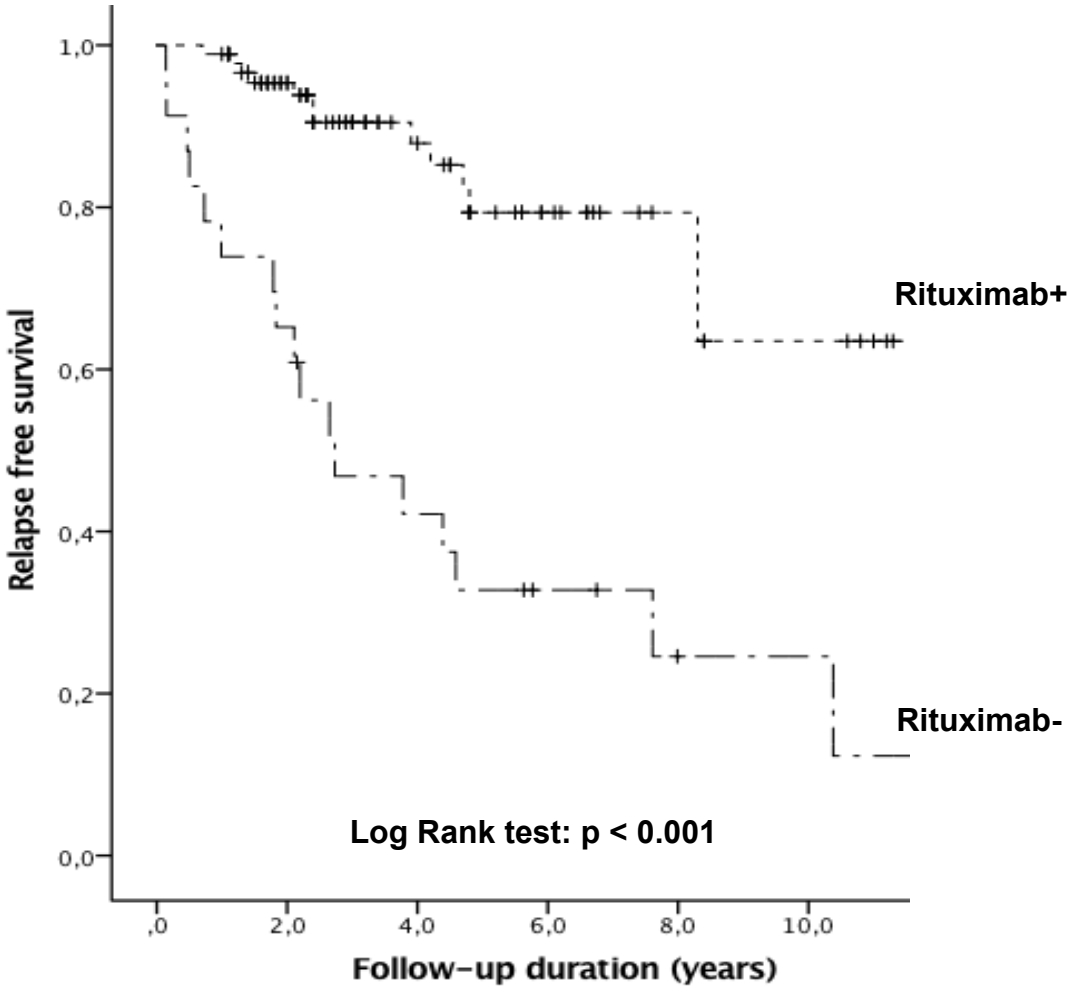
To prevent severe forms… simply prevent relapses

Up to 40% of survivals have a persistent severe (< 10%) ADAMTS13 deficiency after complete remission achievement and are exposed to short-term relapses



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

Don’t forget the most important…

Mrs F… D…, 45 yo

Feb, 15th, 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%...

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

What you need to know to save a patient with iTTP

1. Thrombocytopenia + hemolytic anemia/hemolysis → Schistocytes ? (repeated search) + = iTTP

2. Thrombocytopenia + hemolytic anemia/hemolysis + organ failure (even if schistocytes formerly –) → iTTP

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

Grall et al., Am J Hematol 2017

The triplet regimen: the new standard in iTTP frontline?

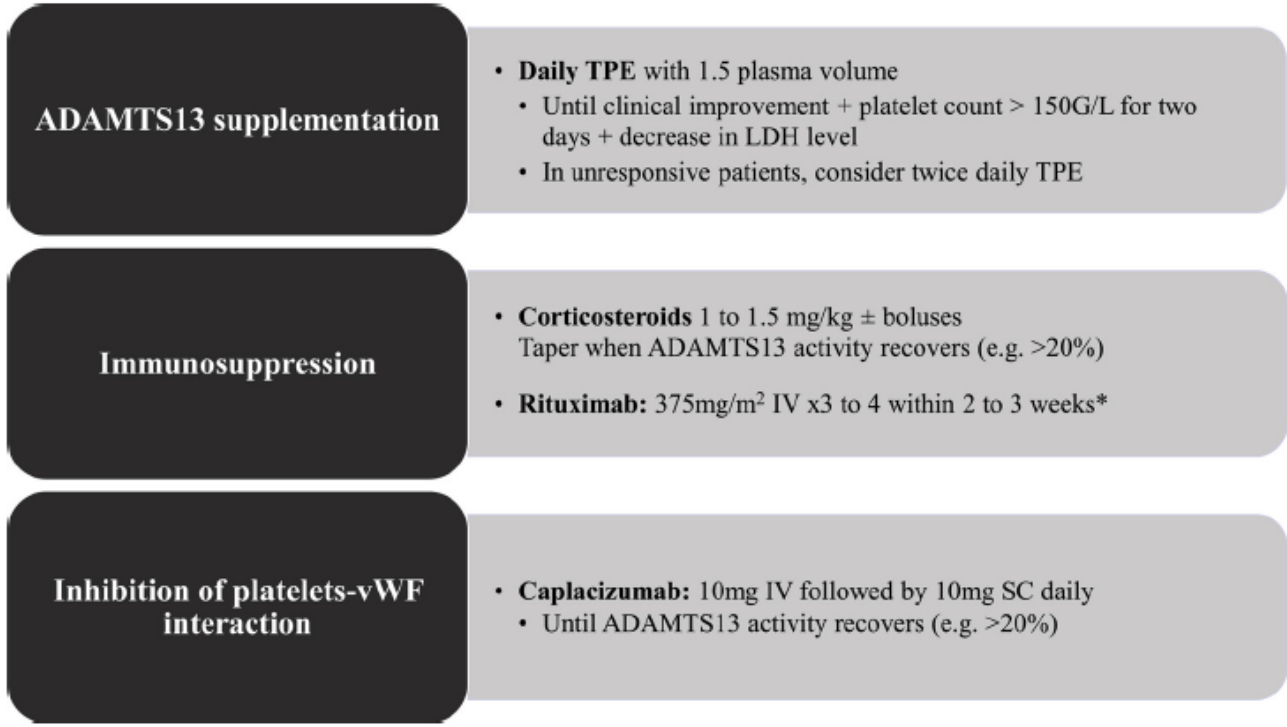


Fig. 1. The three axes of iTTP management in the acute phase.
* Other rituximab administration regimens are currently under investigation.
TPE: Therapeutic plasma exchange. LDH: Lactate dehydrogenase. vWF: von Willebrand factor.

Picod & Coppo, Transf Apherer Sci 2019; Coppo , Cuker & George, Res Pract Thromb Haemost 2018

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. An increasing number of promising therapies are now available in the field of TTP; in the next future, targeted therapies based on anti-vWF agents and rADAMTS13, should help in decreasing TTP early mortality

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

TTP is therefore entering the new era of theragnostic and personalized medicine

The CNR-MAT

Consortium PROFILE (H2020)

MaRIH
Fillière de santé Maladies Rares Immuno-Hématologiques

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

PROFILE