PTT: 100 ans de recherche sur une maladie rare

Paul Coppo

paul.coppo@aphp.fr

AP-HP et Sorbonne Université

MaRIH
Filière de santé Maladies Rares ImmunoHématologiques

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

Reference Center for Thrombotic Microangiopathies

cnr-mat

Réunion d'Hématologie Grand Est – 3 & 4 octobre 2025

Disclosures

1. SANOFI, ALEXION, TAKEDA, TARGED

Member of advisory boards

Honoraria for symposiums

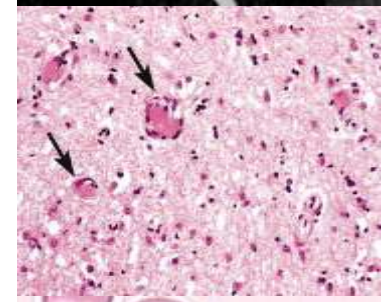
Research grants

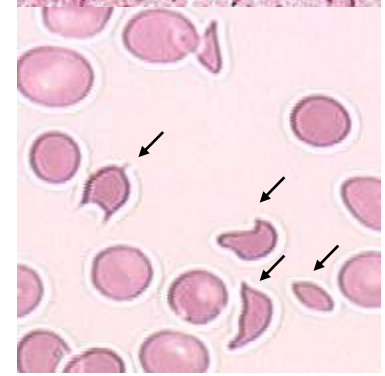
2. The discussion of indications and uses of therapeutic agents during the presentation reflects the opinion of the speaker and may not reflect the views of the industrial partners

PTT: définition

- Thrombopénie profonde
- Anémie hémolytique mécanique
- Défaillances d'organe potentiellement fatales
- Déficit sévère en ADAMTS13

E. Moschcowitz, 1924





Forme congénitale

Période néonatale/post néonatale
Grossesse

< 0.13 cas/10^6 hab/an
85 patients identifiés en France

Forme autoimmune

Femmes jeunes
Rapidement fatale
1-2 cas/10^6 hab/an
> 100 nouveaux patients/an en France

Diagnostic issues in TTP

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

At a time when survival exceeds 98% with current regimens, it is mandatory to make a rapid diagnosis in this potentially fatal disease, to still improve its prognosis

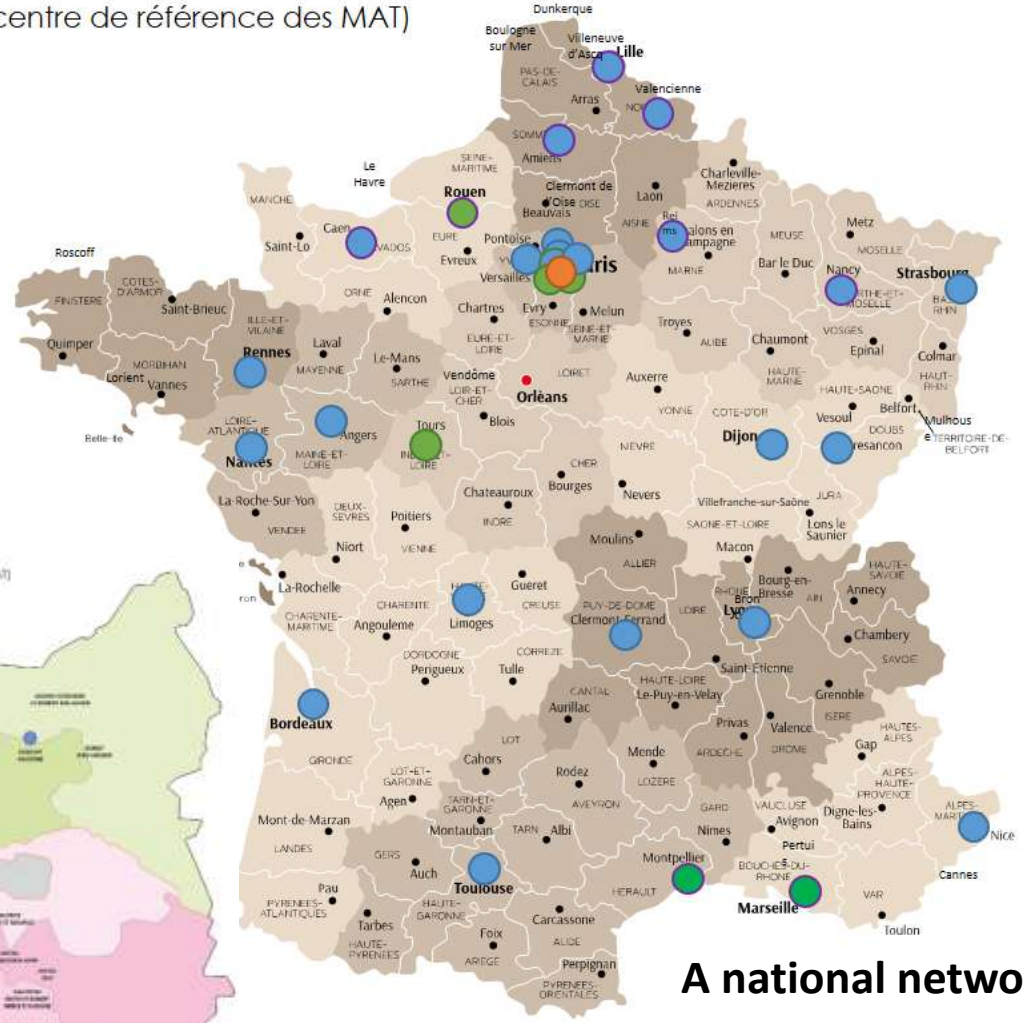
Most of current deaths by TTP result from a diagnostic delay, while death has become exceptional once treatment is started+++

To make clinicians aware of TTP diagnosis with simple algorithms is a major goal to further improve its prognosis

Nom du CRMR : CNR-MAT (centre de référence des MAT)

Filière : MARIH

- Coordonnateur
- Constitutif
- Compétences



Ile-de-France

Reference center (Coordinator)

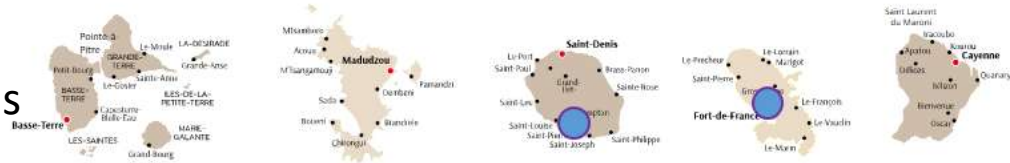
32 expert multidisciplinary centers - Incl. 2 on overseas territories

2 reference labs (ADAMTS13 & Complement)

Patients association

A national network to improve the awareness of clinicians and provide a standardized management and the best standard of care

Territoires ultramarins



PTT autoimmun

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
with no associated condition:

Surrogate markers consistently associated with ADAMTS13 <10%

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

Make a rapid diagnosis to improve prognosis

Features of TMA

MAHA + thrombocytopenia (± organ dysfunction)

No underlying ongoing condition (DIC, cancer, chemo, transplantation, sepsis) (secondary TMA)

Evaluate pretest probability of TTP from platelets and creatinine (e.g., French score, Plasmic score)

Collect serum or plasma for ADAMTS13 testing (+ anti-ADAMTS13 IgG Abs)

While waiting for ADAMTS13 activity, if probability of TTP high:

French score=(1-)2; Plasmic score=(6-)7

or if ADAMTS13 activity is immediately available and <10%

Triplet treatment

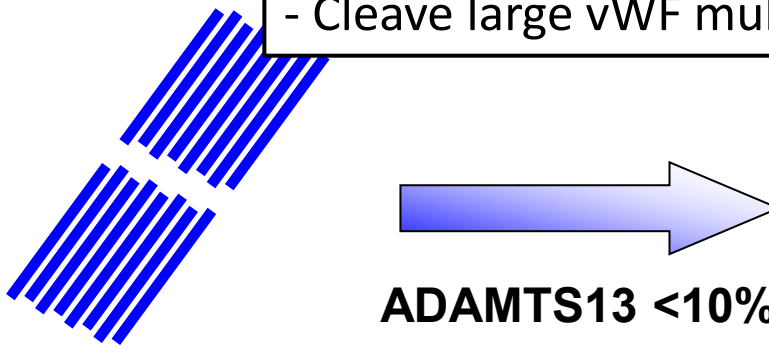
(TPE, immunosuppression, caplacizumab)

Adapted from Zheng et al., J Thromb Haemost 2020 (ISTH recommendations)

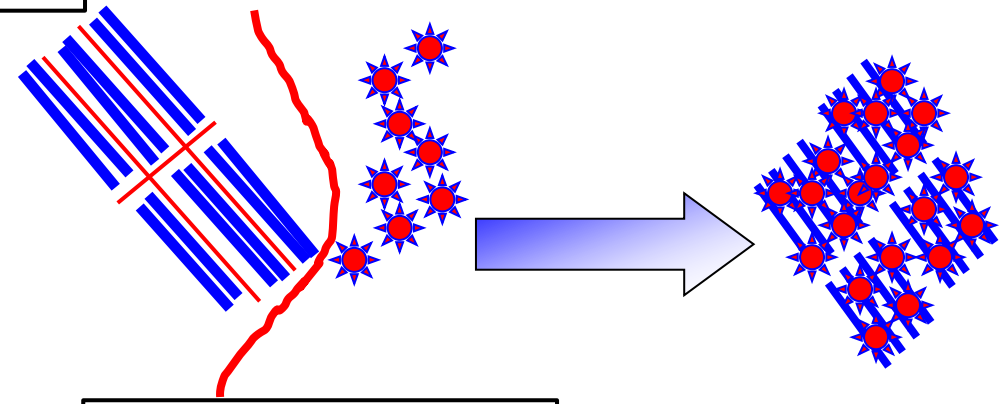
Pathophysiological basis of iTTP treatment

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

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

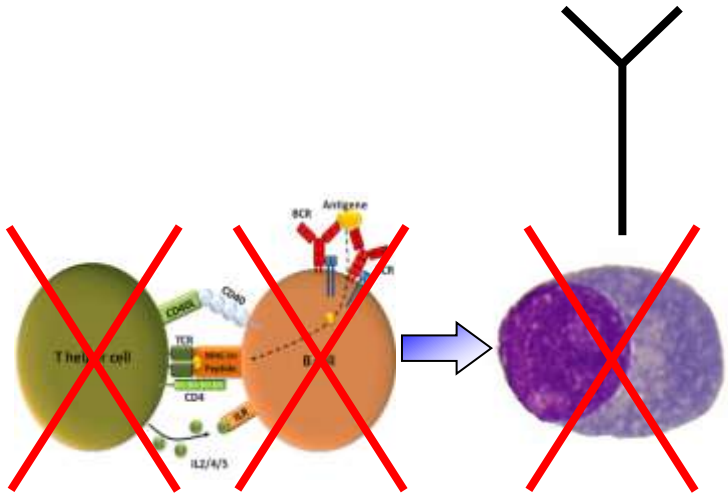


ADAMTS13 <10%



3. Anti-vWF therapies

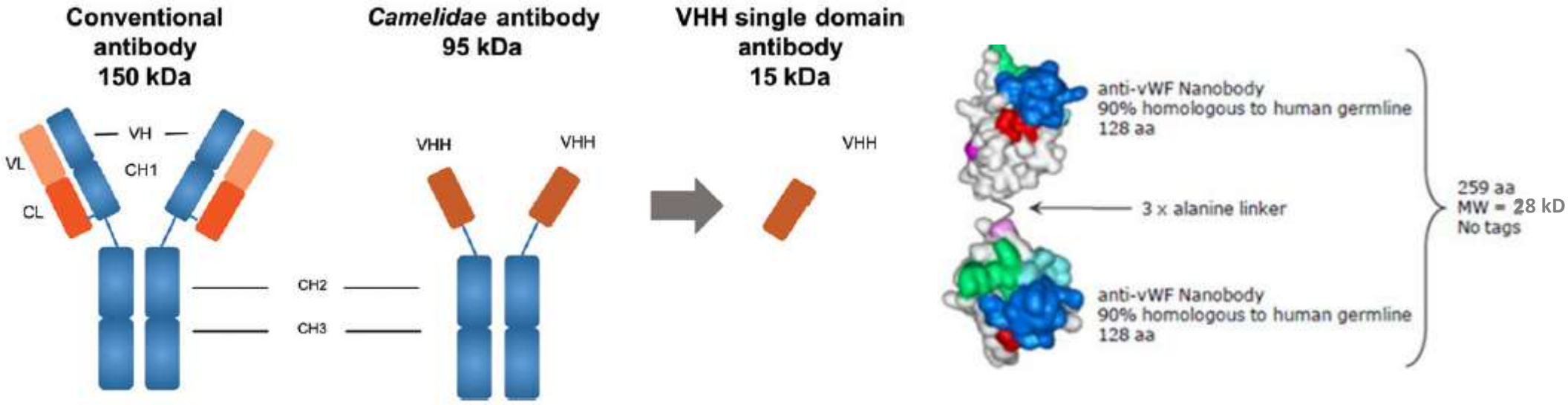
- Inhibitors of vWF-gp1b axis



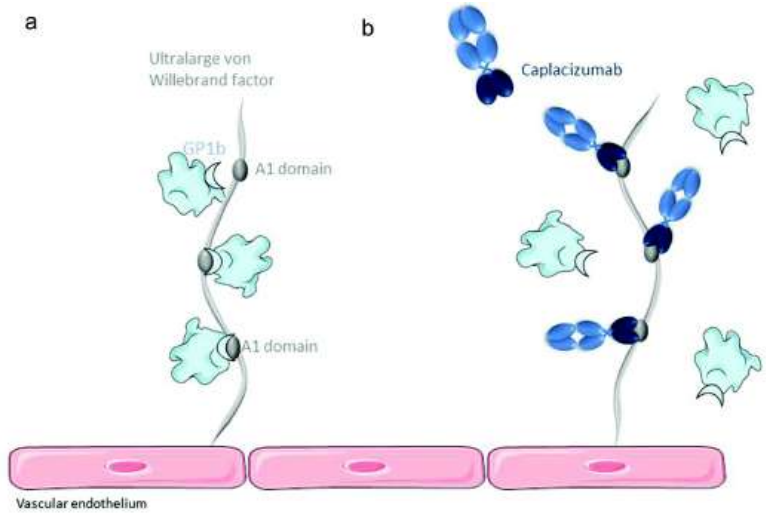
2. Immunomodulation

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

Caplacizumab: a small antibody with big implications for iTTP



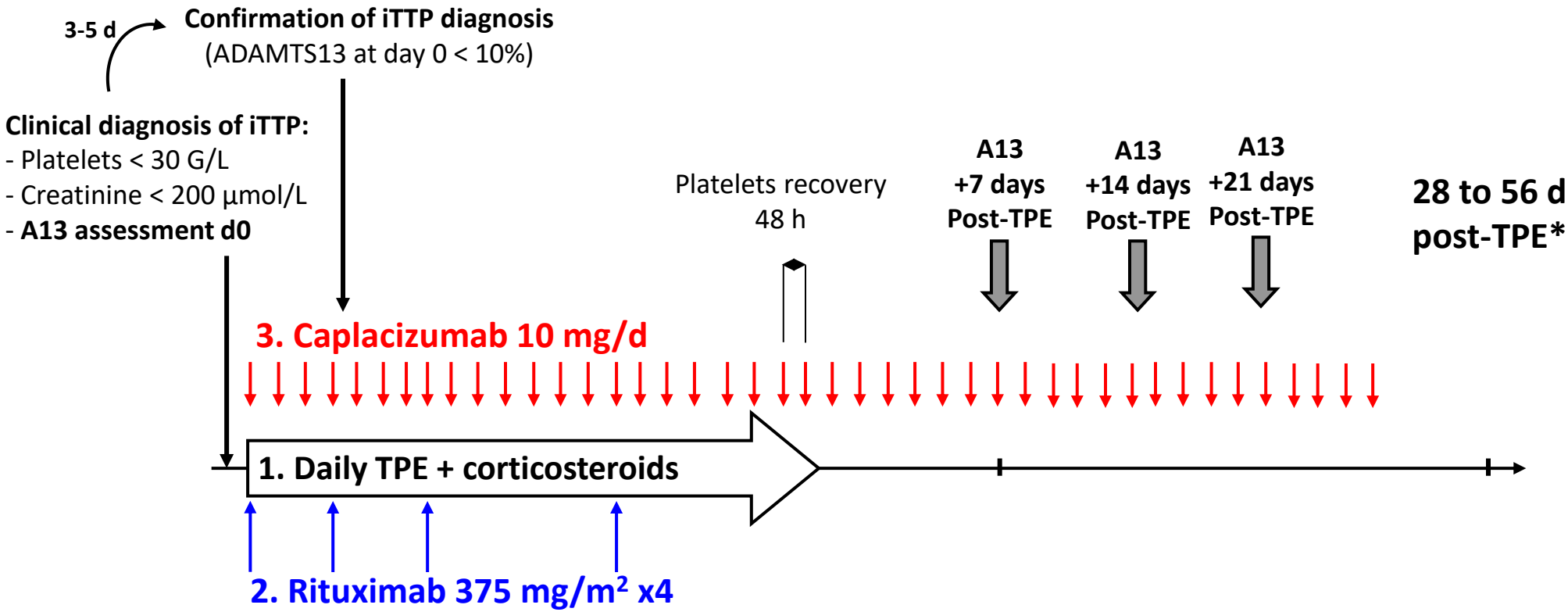
Therapeutic class of proteins derived from the heavy-chain variable domains that occur naturally in heavy-chain Ig from *Camelidae*



Poullin et al., Drugs of Today, 2019; Peyron I, RPTH 2020

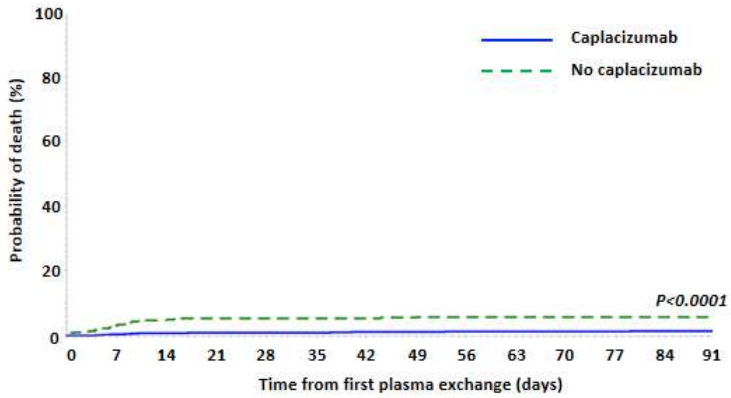
Caplacizumab after the Greec epic: where do we stand?

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



Coppo, Benhamou et al., Blood 2021

Current iTTP prognosis under treatment during acute phase



strategy\ at risk on day	0	7	14	21	28	35	42	49	56	63	70	77	84	91
No caplacizumab	509	496	485	482	482	482	482	481	480	480	480	480	480	480
Caplacizumab	1006	1003	999	998	998	997	995	995	994	994	994	994	993	993

3-month survival: 98.5% vs 94% (p<0.0001)

Mortality is 4.2-fold higher without caplacizumab

	Caplacizumab group (N=1015)	Control group (N=510)	p-value
Clinical response	99%	94%	<0.0001
Refractoriness	1%	10.1%	<0.0001
Time to death from first TPE (days)	11 (9-33)	7 (4-9)	0.01
Time to clinical response (days)	5 (4-8)	6 (4-12)	<0.0001
Number of TPE to achieve clinical response	5 (4-8)	7 (4-16)	<0.0001
Exacerbation rate	4%*	32%	<0.0001

Exacerbation is <u>decreased by 8-fold</u> with caplacizumab

Number of patients needed to treat to prevent:
- **One exacerbation: 3.6**
- **One refractoriness: 11**

Caplacizumab reduces mortality at the acute phase

Number of patients needed to treat : 22

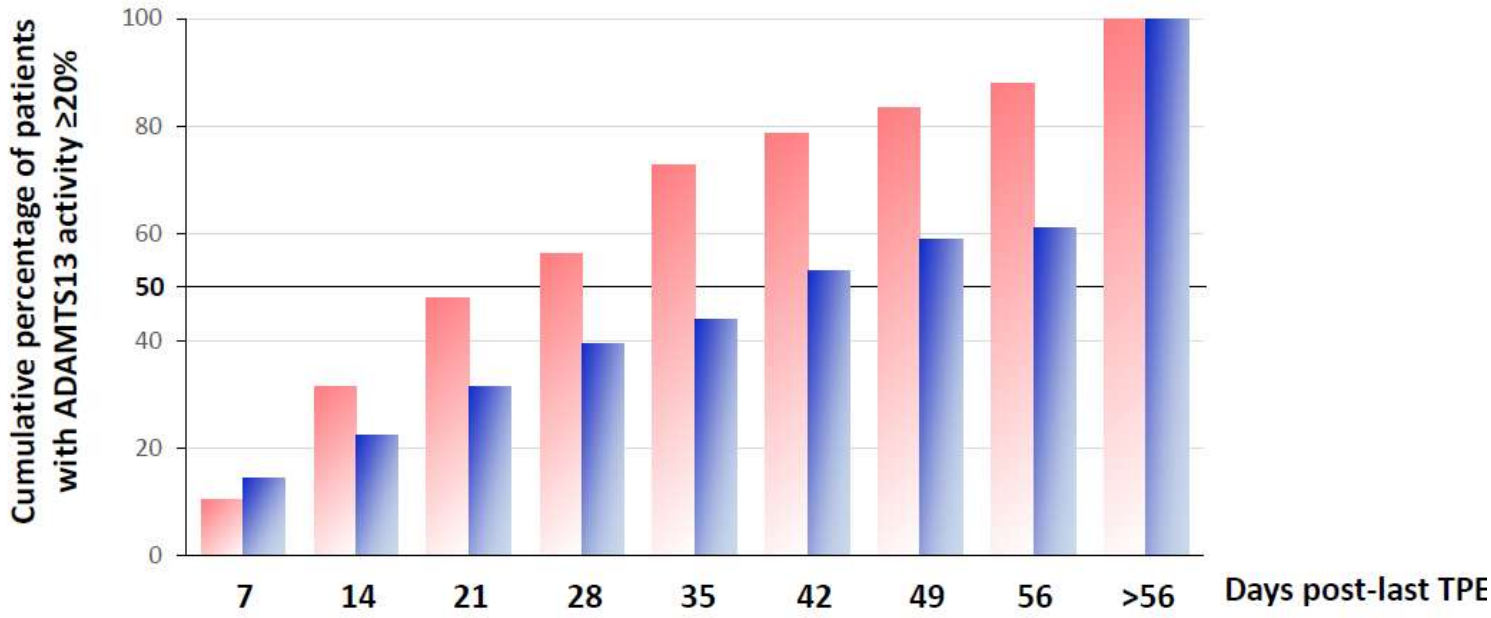
Faster clinical response
less exacerbations and refractoriness

We are now in a logic of therapeutic de-escalade with PEX-free regimens…

(shortened length of hospitalization/probably less therapy-related morbidity)

IWG-TTP, EClinicalMedicine 2025; MAYARI trial results; ISTH 2025

Time to ADAMTS13 activity Improvement (i.e., activity ≥ 20%)



Triplet regimen cohort

Historical treatment cohort

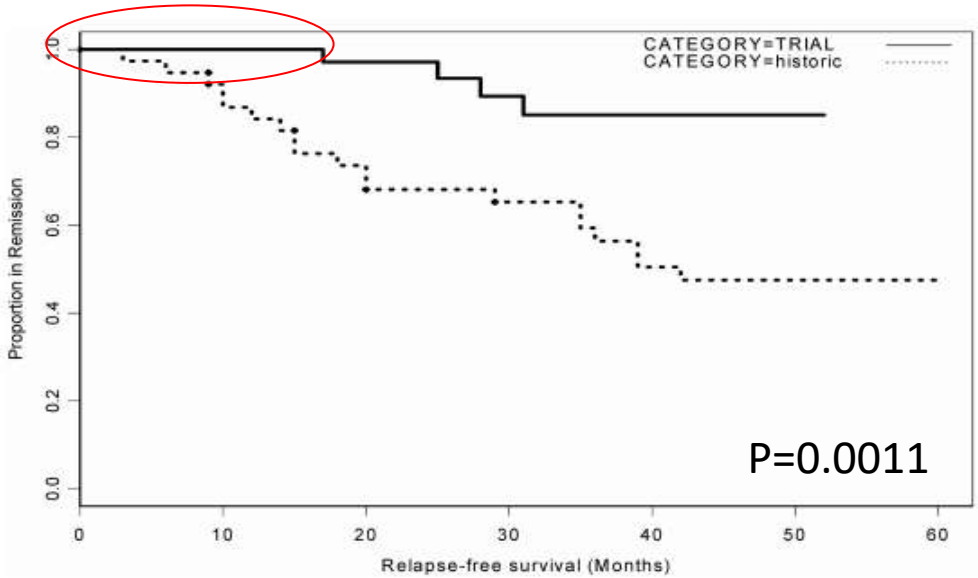
10% in the triplet regimen improve ADAMTS13 activity > D56…

How to identify long-term responders earlier?

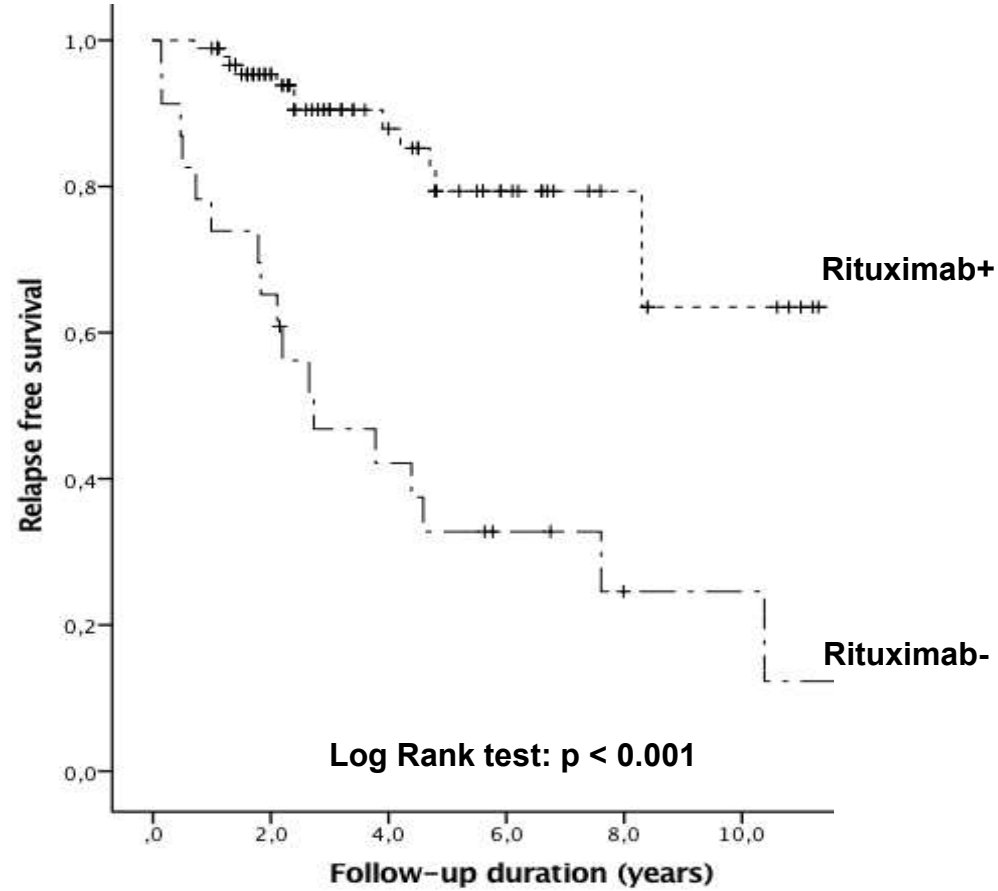
Coppo, Benhamou et al., Blood 2021

Prevention of iTTP relapses for virtually all patients

Acute phase



Long-term follow-up



In the (rare) remaining patients unresponsive or intolerant to rituximab, obinutuzumab is efficient and safe

Scully et al., Blood 2011; Hie et al., Blood 2014; Jestin et al., Blood 2018; Weisinger et al., Br J Haematol 2025

Le futur: un traitement « PEX-free » ?

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

PEX-free regimens provide rapid and sustained clinical response in iTTP

Parameter	TPE-free cohort (n=42)	TPE cohort (n=59)	P
Median age (range)	43 (20-83)	47 (20-80)	.43
Female / male sex No. (%) Data missing	31 (75.6) / 10 (24.4) 0 (0)	40 (67.8) / 17 (28.8) 2 (3.4)	.82
BMI – mean (range), kg/m²	29 (17-50)	28 (20-46)	.62
First iTTP episode / iTTP relapse No. (%) Data missing	25 (59.5) / 17 (40.5) 0 (0)	38 (64.4) / 18 (30.5) 3 (5.1)	.40
Median platelet count (range), x10⁹/L	16 (4-127)	12 (3-52)	.09
Median lactate dehydrogenase (range), U/L	703 (214-2500)	1052 (373-3467)	< .01
Initial troponin Elevated – no. (%) Not elevated – no. (%) Data missing	16 (38.1) 11 (26.2) 15 (35.7)	27 (45.8) 8 (13.6) 24 (40.7)	.17
Median serum creatinine (range), mg/dL	0.95 (0.57-5.30)	1.07 (0.5-3.65)	.07
ADAMTS13 activity < 10% – no. (%)	42 (100)	58 (98.3)†	>.99
Glasgow Coma Scale – no. (%) 15 <15 Data missing	38 (90.5) 4 (9.5) 0 (0)	43 (72.9) 11 (18.6) 5 (8.5)	.17
Neurological symptoms upon admission – no. (%) Patients with at least one neurological symptom Aphasia / Dysarthria Blurred vision Coma Headache Focal deficiency Paresthesia Seizure Confusion	24 (57.1) 4 (9.5) 4 (9.5) 0 (0) 7 (16.7) 4 (9.5) 4 (9.5) 1 (2.4) 8 (19.0)	26 (44.1) 8 (13.6) 3 (5.1) 2 (3.4) 4 (6.8) 5 (8.5) 3 (5.1) 3 (5.1) 10 (16.9)	.23
French Severity Score – no. (%) Low (0-1) Intermediate (2) High (3-4) Data missing	27 (64.3) 10 (23.8) 5 (11.9) 0 (0)	30 (50.8) 15 (25.4) 6 (10.2) 8 (13.6)	.90

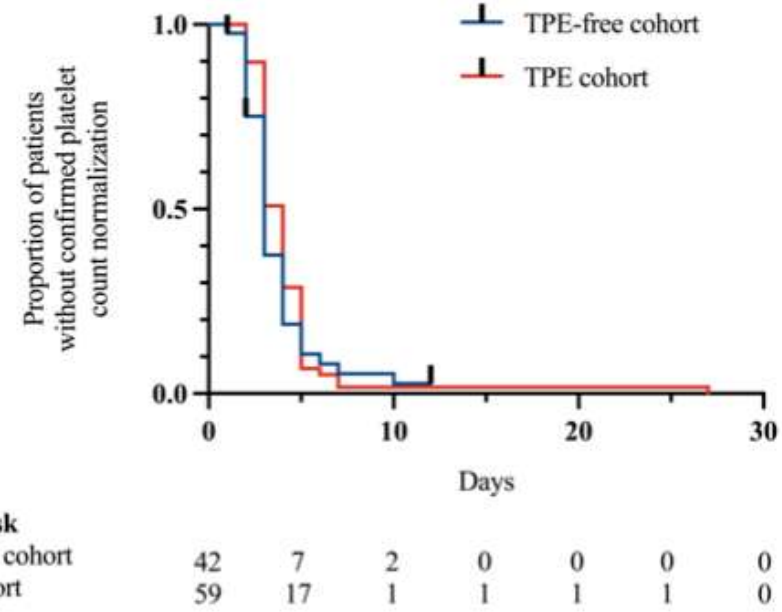
Relatively small number of patients (N=42); not all the severity spectrum of the disease is represented

More relapsers (40%) in the PEX-free cohort:

- ADAMTS13 easily anticipated

- tighter follow-up; relapse more rapidly anticipated

Figure 2. Time to platelet count normalization after the first caplacizumab administration. Symbols indicate censored data. P value for time to platelet count normalization is 0.31 according to log-rank test.



Kühne et al., Blood 2024

PTT congénital

Traitement = perfusions de plasma

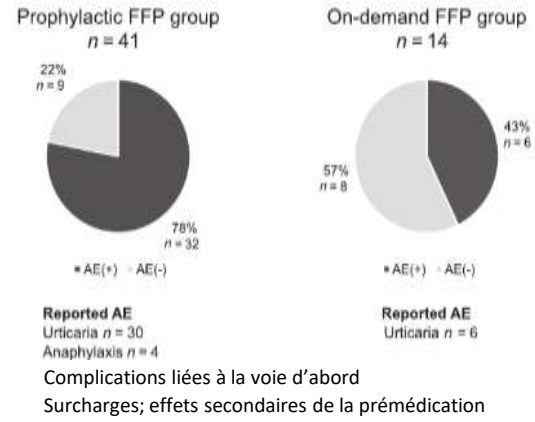
Permettent l'apport exogène d'ADAMTS13 (l'enzyme manquante): 5-10 ml/kg/2-3 sem

Octaplas® a l'AMM pour le traitement du PTT (dans le cadre des échanges plasmatiques)

Procédure lourde (hospitalisations régulières, effets secondaires): QV impactée

VS

Les effets secondaires sont fréquents



Complications liées à la voie d'abord

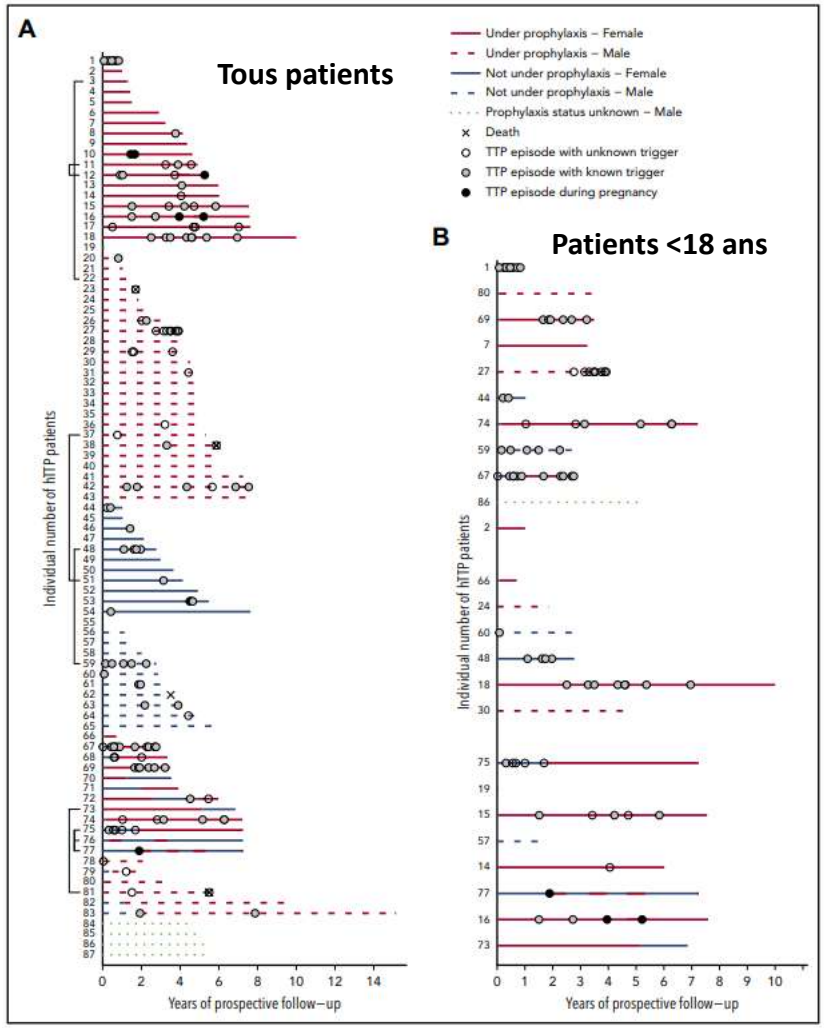
Surcharges; effets secondaires de la prémédication

Cause de sous-traitement

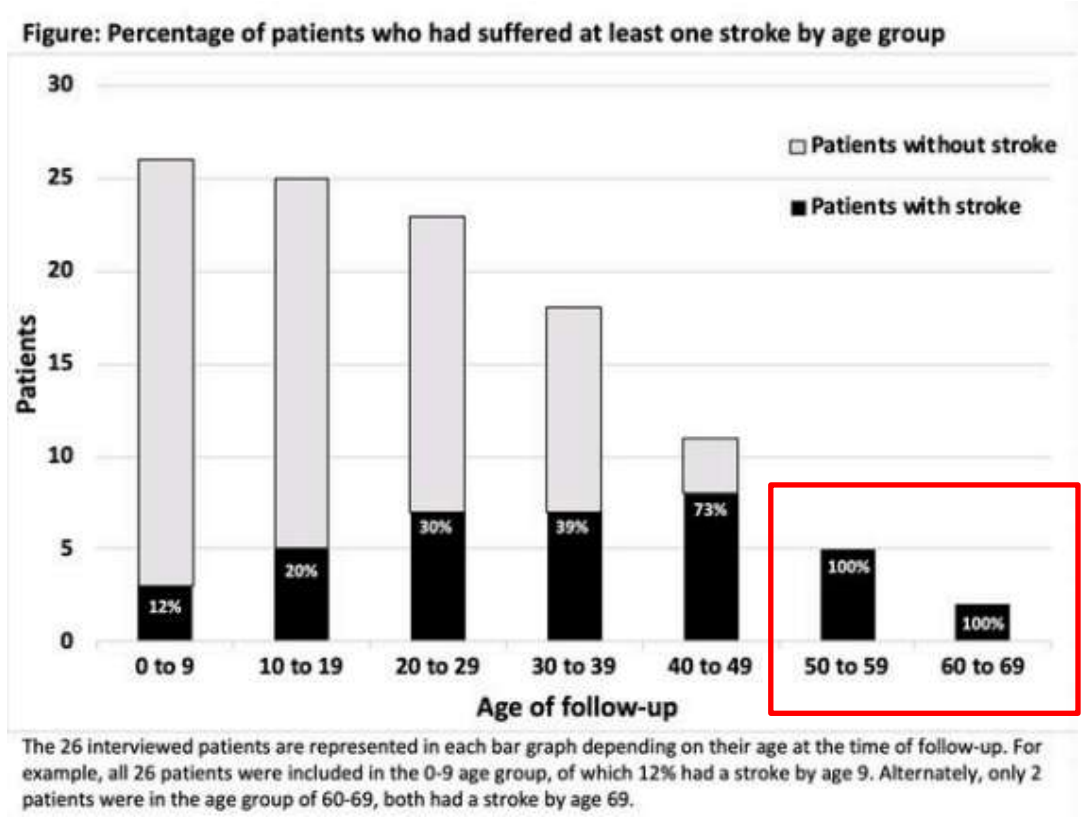
Nécessité d'alléger le traitement

Antoine et al., Br J Haematol 2003; Sakai et al., Br J Haematol 2021; Tarasco et al., Blood 2021

L’apport d’ADAMTS13 via le plasma est insuffisant



Les rechutes de PTT surviennent chez les femmes et les hommes, malgré le traitement; impact fonctionnel important



Exemple de l’atteinte cérébrale: AVC ischémiques chez 16 pts (62%)
Age médian de survenue du 1er AVC: 26 ans (Nouveaux-nés – 53 ans)

Le plasma reste un traitement par défaut; ainsi le besoin médical est partiellement couvert

Tarasco et al., Blood 2021; Sakai et al., Br J Haematol 2021; Borogovac et al., Blood 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Recombinant ADAMTS13 in Congenital Thrombotic Thrombocytopenic Purpura

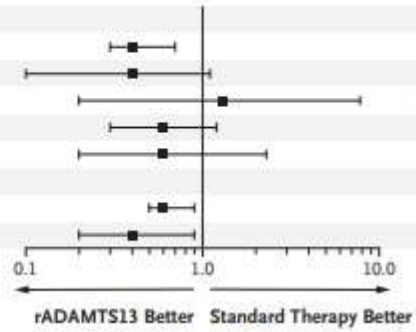
Marie Scully, M.D., Ana Antun, M.D., Spero R. Cataland, M.D., Paul Coppo, M.D., Ph.D., Claire Dossier, M.D., Nathalie Biebuyck, M.D., Wolf-Achim Hassenpflug, M.D., Karim Kentouche, M.D., Paul Knöbl, M.D., Johanna A. Kremer Hovinga, M.D., M. Fernanda López-Fernández, M.D., Ph.D., Masanori Matsumoto, M.D., Ph.D., Thomas L. Ortel, M.D., Ph.D., Jerzy Windyga, M.D., Ph.D., Indranil Bhattacharya, Ph.D., Michael Cronin, Pharm.D., Hong Li, Ph.D., Björn Mellgård, M.D., Ph.D., Munjal Patel, Ph.D., Parth Patwari, M.D., Sc.D., Shan Xiao, Ph.D., Pinghai Zhang, M.D., Ph.D., and Linda T. Wang, M.D., for the cTTP Phase 3 Study Investigators*

Etude pivot de phase 3 – rADAMTS13 vs traitement standard; N=48 pts

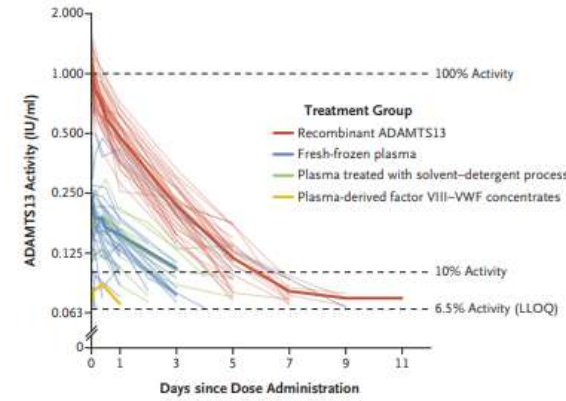
6 mois de traitement -> cross-over de 6 mois

Puis 6 mois de traitement avec rADAMTS13 pour tous

Outcome	rADAMTS13	Standard Therapy	Estimated Ratio (95% CI)
	least-squares mean annualized incidence rate (95% CI)		
Prespecified TTP manifestations			
Thrombocytopenia	0.74 (0.37–1.50)	1.73 (0.92–3.23)	0.4 (0.3–0.7)
Elevated LDH level	0.26 (0.10–0.72)	0.74 (0.38–1.44)	0.4 (0.1–1.1)
Increased creatinine level	0.10 (0.02–0.47)	0.08 (0.02–0.36)	1.3 (0.2–7.8)
Neurologic symptoms	0.18 (0.06–0.51)	0.29 (0.11–0.78)	0.6 (0.3–1.2)
Abdominal pain	0.11 (0.03–0.39)	0.17 (0.06–0.52)	0.6 (0.2–2.3)
Exploratory outcomes			
Composite TTP manifestations	2.28 (1.35–3.88)	3.68 (2.23–6.08)	0.6 (0.5–0.9)
Other TTP manifestations	0.32 (0.14–0.72)	0.81 (0.44–1.49)	0.4 (0.2–0.9)



60% de thrombopénies en moins



No. of Patients						
Recombinant ADAMTS13	36	39	34	31	13	3
Fresh-frozen plasma	23	27	11	2		1
Plasma treated with solvent–detergent process	7	9	5	3		
Plasma-derived factor VIII–VWF concentrates	2	1				

Figure 3. Time Series of ADAMTS13 Activity after Intravenous Administration of Recombinant ADAMTS13 and Standard Therapy.

Data are from adults and adolescents in the pharmacokinetic full analysis population. ADAMTS13 activity was measured after a single, 40-IU-per-kilogram dose of recombinant ADAMTS13 as part of the PK-I assessment. The individual ADAMTS13 activity (fine lines) and mean activity grouped according to treatment type (thick lines) are plotted on a logarithmic scale. An ADAMTS13 activity of 1 IU per milliliter represents 100% (top dashed horizontal line), and the lower limit of quantification (LLOQ) for the assay was 6.5% (bottom dashed horizontal line). VWF denotes von Willebrand factor.

Accès précoce pré-AMM obtenu le 9 février 2024;

programme débuté le 18 mars

Exposition à ADAMTS13 avec rADAMTS13 vs SOC: 5 fois plus importante (en concentration et en durée)

Pourquoi les patients atteints de PTT meurent-ils encore…?

Mrs D… S…, 44 yo

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

Past medical history:

- vitamin B12 deficiency in the sister

History:

- Blood cell count and serum creatinine normal on August, 2020
- July, 10th 2021: « black » urines with hematuria; an episode of chills, with lumbar pain
- July, 11th : referred to the 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 slightly decreased)
- TMA (TTP or HUS) (but no renal failure or CNS involvement) (ADAMTS13 sampled on July, 15th)
- Autoimmune thrombocytopenia
- Atypical Evans' syndrome

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 (apparently normal)
  11.40 am: bradycardia, electro-mecanic dissociation and death

iTTP (ADAMTS13 <5%; obtained post-mortem)

A statement: fulminant deaths around diagnosis do not seem to improve

	Death before treatment initiation	Death after treatment initiation
2005 - 2009	2.4%	12.9%
2010 - 2014	3.7%	7.2%
2015 - 2019	2.2%	4%
2020 - 2024	2%	1%

Caplacizumab

No clear improvement

Outstanding decrease of death under treatment

Context analysis:

Diagnostic delay? Atypical presentation? Wrong or delayed treatment? Associated comorbidities? None of these?

Patients with iTTP are exposed to a risk of sudden death and need immediate protection

CNR-MAT, unpublished results

What you need to know to save a patient with TTP

A pre-requisite: put the « pentad » to the trash of History

Diagnosis of TTP: a « pentad »

- Cerebral involvement
- Renal failure
- Fever
- MAHA
- Thrombocytopenia

Highly specific…
but completely non sensitive

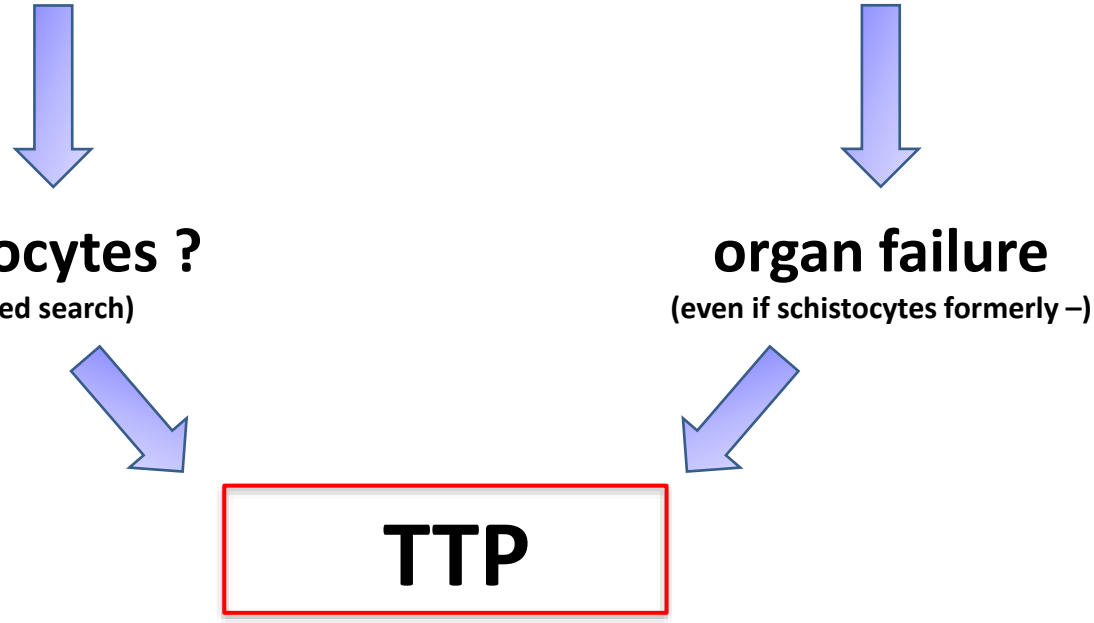
Late diagnosis, pre-mortem condition……..

An early diagnosis, by improving sensitivity (even if detrimental for specificity) is mandatory

Amorosi & Ultmann, Medicine 1966

What you need to know to save a patient with iTTP

1. Thrombocytopenia + hemolytic anemia/hemolysis

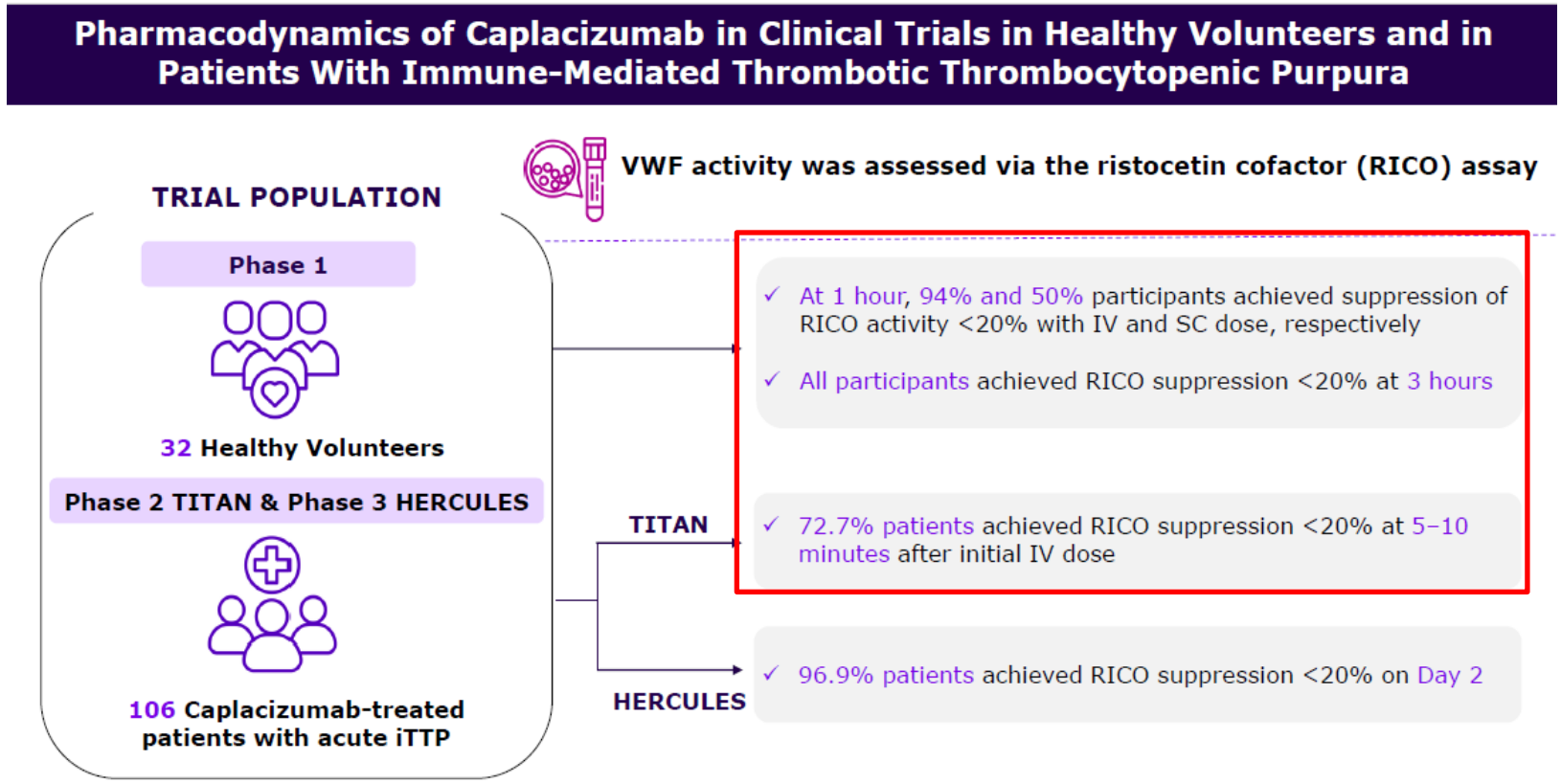


2. Refer the patient to/contact a trained team for treatment immediately

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

Pharmacodynamics of caplacizumab in healthy volunteers and Phase II/III trial patients with immune-mediated thrombotic thrombocytopenic purpura

Paul Coppo,[1] Marie Scully,[2] Javier de la Rubia,[3,4] Flora Peyvandi,[5,6] Spero Cataland,[7] Paul Knoebl,[8] Katerina Pavenski,[9] Umer Khan,[10] Sriya Gunawardena,[11] Ana Paula Marques[12]



Caplacizumab inhibits ~immediately VWF-platelet interaction and thrombi neoformation; provides relevance for the IV pre-TPE administration

Manuscript in preparation

Protocole national de diagnostic et de soins (PNDS)

Purpura thrombotique thrombocytopénique

Ce PNDS a été coordonné par le Pr Paul COPPO du Centre de référence des microangiopathies thrombotiques (CNR-MAT) de l'hôpital Saint-Antoine, en collaboration avec le Pr Agnès VEYRADIER de l'hôpital Lariboisière, et le Pr Ygal BENHAMOU de l'hôpital de Rouen sous l'égide de la filière de santé maladies rares MARIH (Maladies Rares Immuno-Hématologiques).

Ce document est soutenu par la Société Française d'Hématologie (SFH), la Société Nationale Française de Médecine Interne (SNFMI) et le Groupe d'Etude Hémostase et Thrombose (GEHT).

Octobre 2022

Conclusion

1. A travers un siècle de progrès, le PTT représente un exemple illustratif du succès de la médecine translationnelle, où la recherche fondamentale a fonctionné en synergie avec la recherche clinique pour le bénéfice des patients

2. Le caplacizumab et la protéine ADAMTS13 recombinante, issus de cette dynamique, ont/vont transformer le pronostic et la prise en charge du PTT, et devraient encore aboutir à alléger la charge de soin (régimes thérapeutiques « PEX-free » en cours d'évaluation; traitement à domicile)

3. Il est important d'informer les cliniciens de l'importance du diagnostic précoce dans le PTT congénital (limiter l'errance diagnostique+++) et d'une prise en charge optimale pour prévenir les séquelles à long terme

4. Sensibiliser les cliniciens au diagnostic de PTT reste un enjeu majeur à l'ère des thérapies ciblées; la majorité des décès par PTT résultent d'un retard de prise en charge ou d'une prise en charge inadaptée

5. Avec les nouvelles thérapies ciblées en cours et à venir, le PTT est aussi devenu un exemple de maladie coûteuse…; il est nécessaire de permettre l'accès aux meilleures thérapies pour tous dans le monde, pas seulement aux plus chanceux

Le CNR-MAT

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

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

TOLERAGE