PTT: l'innovation comme clé pour améliorer la prise en charge des patients

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

Congrès français d'Hémostase – Symposium TAKEDA - 2023

Conflits d’intérêt

SANOFI, ALEXION, TAKEDA, JANSSEN

Member of advisory boards

Honoraria for symposiums

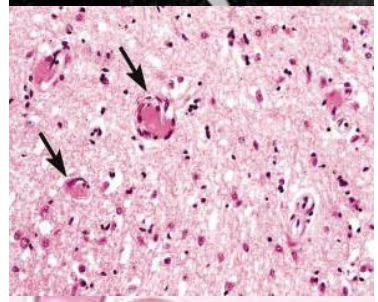
Research grants

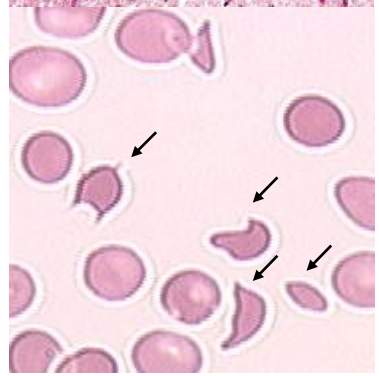
Cette présentation a pour objectif d'apporter des informations médicales et scientifiques permettant au professionnel de santé qui en fait la demande d’établir ses propres conclusions. Takeda France ne recommande pas l’utilisation de ses produits en dehors des indications approuvées par l’Autorisation de Mise sur le Marché.

PTT: définition – Présentation clinique

- **Thrombopénie profonde périphérique (< 30 G/L)**
- **Défaillance d'organe de sévérité variable**
- **Anémie hémolytique mécanique**
- **Déficit sévère en ADAMTS13**

E. Moschcowitz, 1924





Congénital

(Upshaw-Schulman syndrome)

Période néonatale/post néonatale
Grossesse

< 0.13 cas / 10^6 hab /an

Autoimmun

Femmes jeunes en âge de procréer
Spontanément fatal
1-2 cas/10^6 hab/an
> 100 nouveaux patients/an

Les débuts du traitement…

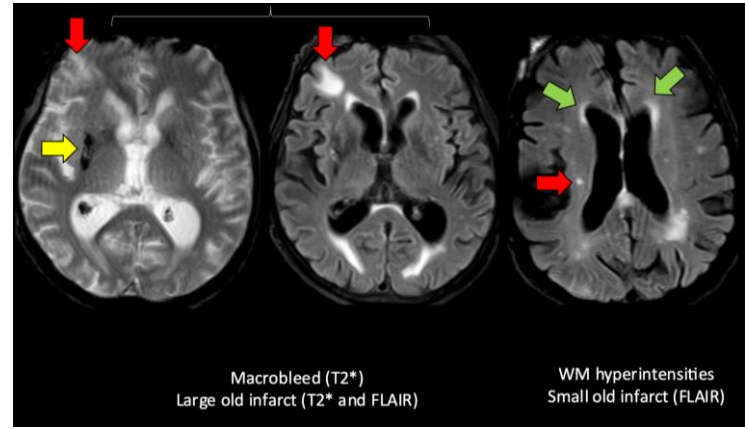
1975. Homme de 27 ans. AVC ischémique avec convulsion puis coma.

Thrombopénie 15 K/L; anémie 6 d/dL; LDH 3xN; schizocytes +++; créatinine au plus haut 216 µmol/L

Traitement:

Corticostéroïdes, persantine, aspirine ;

Splénectomie, transfusion de plaquettes ⇨ **« Rescapé… »**



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THROMBOTIC THROMBOCYTOPENIC PURPURA: REPORT OF 16 CASES AND REVIEW OF THE LITERATURE[1, 2]

EDWARD L. AMOROSI, M.D.[3] AND JOHN E. ULTMANN, M.D., F.A.C.P.[4]

VI. PROGNOSIS AND THERAPY

Thrombotic thrombocytopenic purpura usually runs a rapidly progressive and fatal course and the majority of patients die within three months of onset of the disease (Table VIII). It is not possible, however, to predict with certainty the outcome or duration of illness in an individual case due to the occasional more chronic form of the disease (33). It should be noted that frequently patients with a long illness prior to hospitalization died shortly after admission and others with severe neurologic or hemorrhagic manifestations on admission lived many months or years after the presenting symptoms and signs.

Twenty-seven patients included in this review were still alive at the time of reporting. Ten of these cases, however, represent examples

N=246 patients;

26 survivants (10,5%), dont 10 SHU probables…

HISTORIQUE

<u>1924</u> : **premier cas rapporté de PTT**

transfusions érythrocytaires

Moschcowitz et al., 1924

<u>1959</u> : **efficacité des échanges de sang total**

Rubenstein et al., 1959

<u>1977</u> : **échanges transfusionnels sans plasma inefficaces; le plasma seul reste efficace**

Byrnes et al., 1977

Déficit en un composant du plasma

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

Les révolutions de la fin des années '90

blood

Partial Purification and Characterization of a Protease From Human Plasma Cleaving von Willebrand Factor to Fragments Produced by In Vivo Proteolysis

blood

Physiologic Cleavage of von Willebrand Factor by a Plasma Protease Is Dependent on Its Conformation and Requires Calcium Ion

By Han-Mou Tsai

The New England Journal of Medicine

VON WILLEBRAND FACTOR–CLEAVING PROTEASE IN THROMBOTIC THROMBOCYTOPENIC PURPURA AND THE HEMOLYTIC–UREMIC SYNDROME

MIHA FURLAN, PH.D., RODOLFO ROBLES, MIRIAM GALBUSERA, SC.D., GIUSEPPE REMUZZI, M.D., PAUL A. KYRLE, M.D., BRIGITTE BRENNER, MANUELA KRAUSE, M.D., INGE SCHARRER, M.D., VOLKER AUMANN, M.D., UWE MITTLER, M.D., MAX SOLENTHALER, M.D., AND BERNHARD LÄMMLE, M.D.

ANTIBODIES TO VON WILLEBRAND FACTOR–CLEAVING PROTEASE IN ACUTE THROMBOTIC THROMBOCYTOPENIC PURPURA

HAN-MOU TSAI, M.D., AND ERIC CHUN-YET LIAN, M.D.

Mutations in a member of the *ADAMTS* gene family cause thrombotic thrombocytopenic purpura

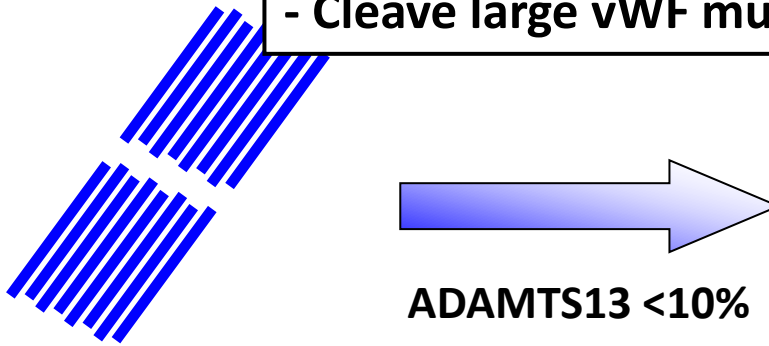
Gallia G. Levy*, William C. Nichols†, Eric C. Lian‡, Tatiana Foroud§, Jeanette N. McClintick§, Beth M. McGee*, Angela Y. Yang*, David R. Siemieniak*, Kenneth R. Stark*, Ralph Gruppo‖, Ravindra Sarode¶, Susan B. Shurin#, Visalam Chandrasekaran☆, Sally P. Stabler**, Hernan Sabio††, Eric E. Bouhassira‡‡, Jefferson D. Upshaw, Jr§§, David Ginsburg* & Han-Mou Tsai‖‖

It all becomes clear…

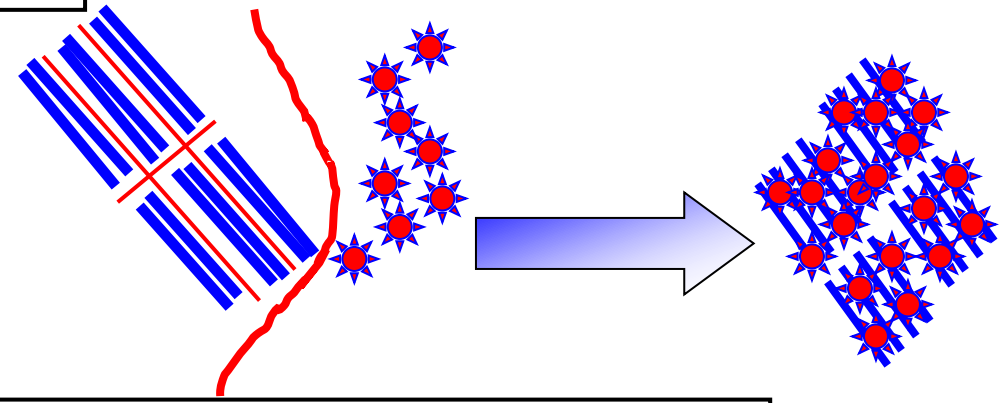
Pathophysiological basis of TTP treatment

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

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

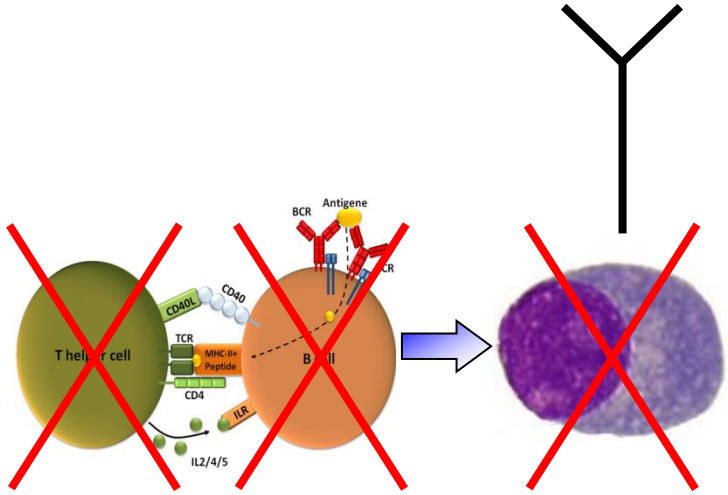


ADAMTS13 <10%



3. Inhibition of platelet-vWF interaction

- Inhibitors of vWF-gp1b axis



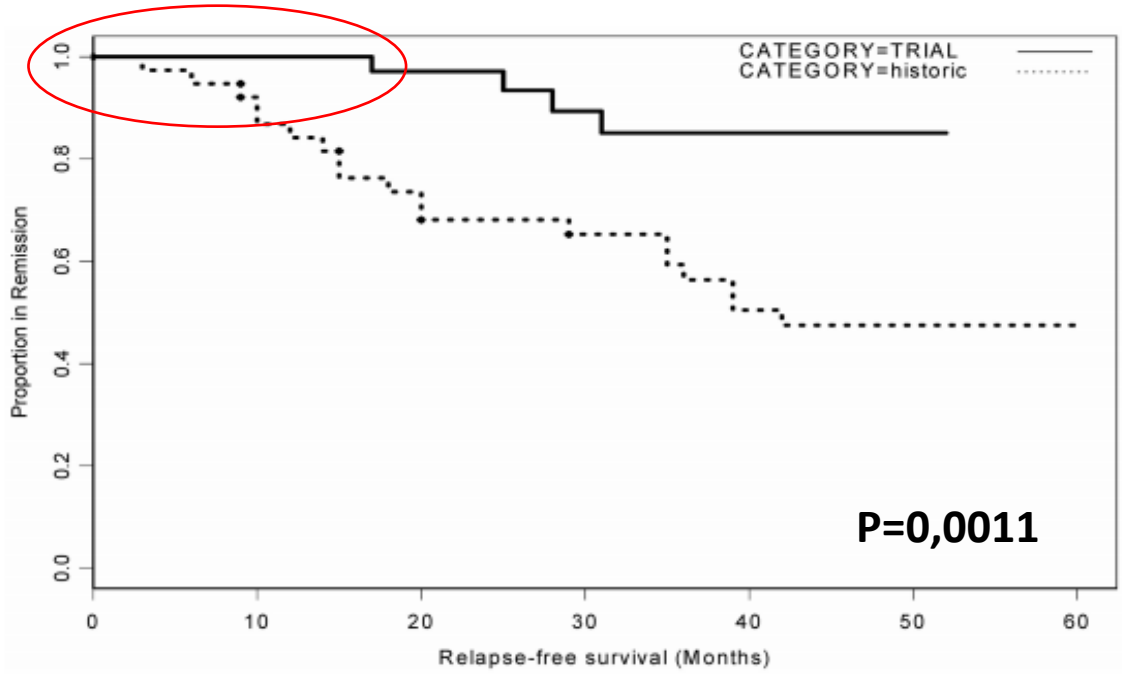
2. Immunomodulation

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

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

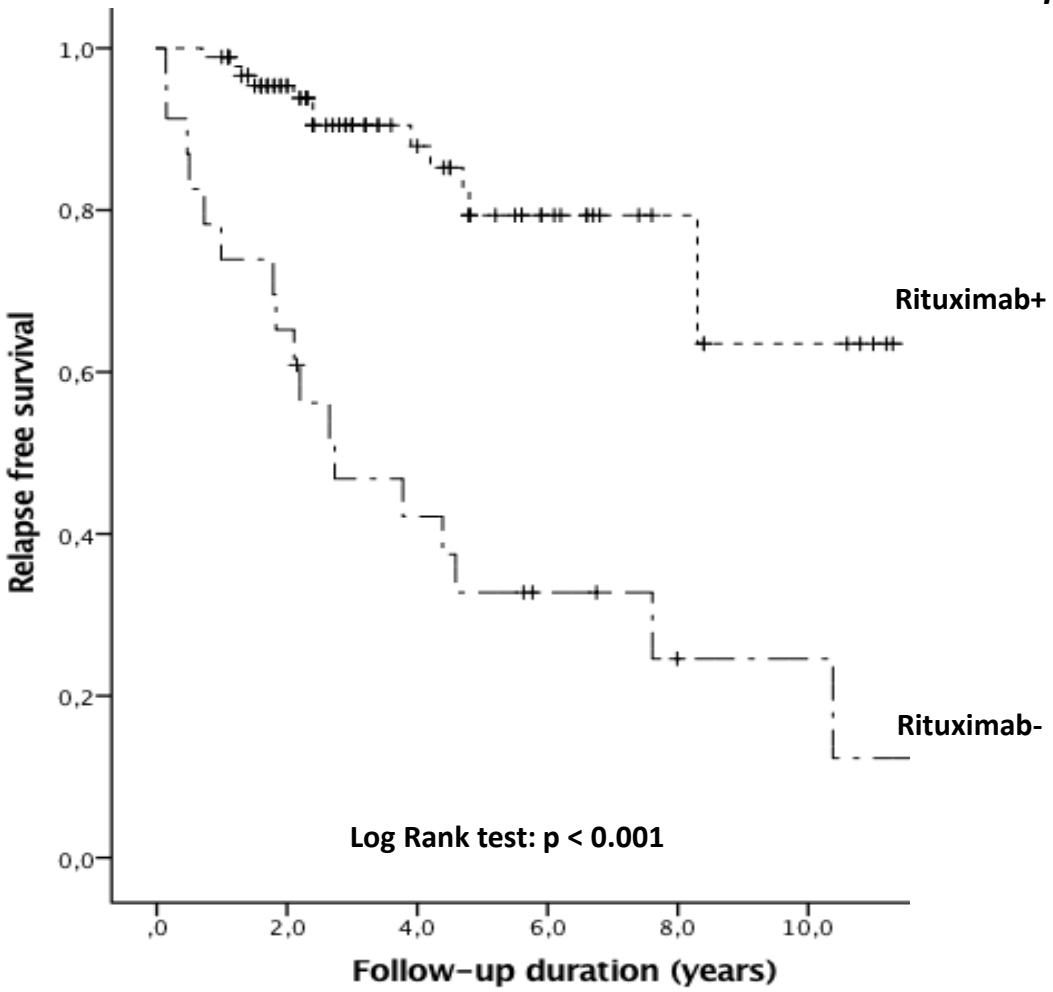


40% of patients w/o RTX remain with an undetectable (<10%) ADAMTS13 activity after the acute phase, and

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

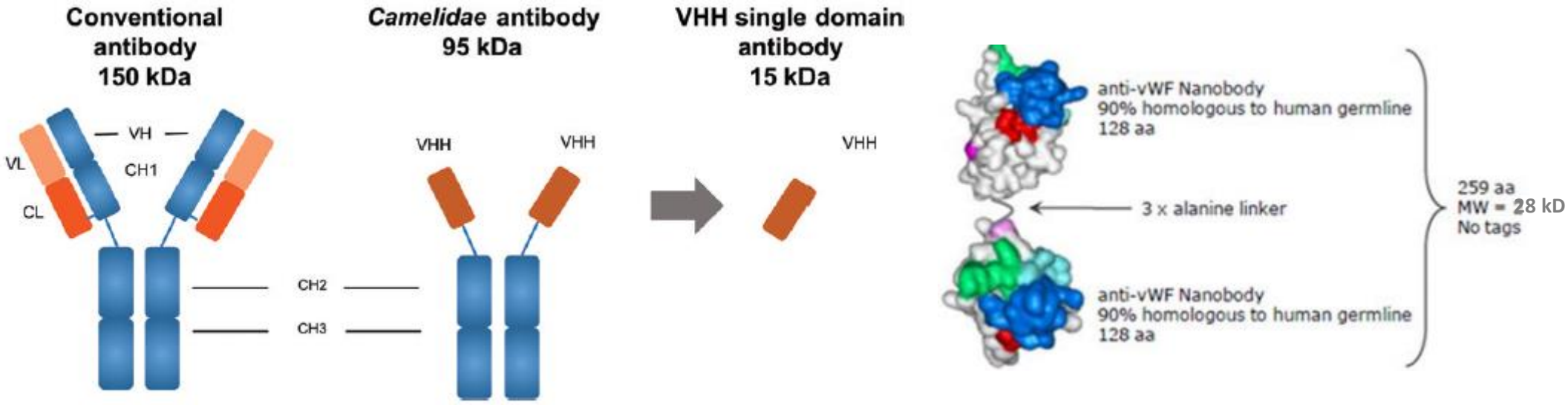
Rituximab: the guardian angel of ADAMTS13

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

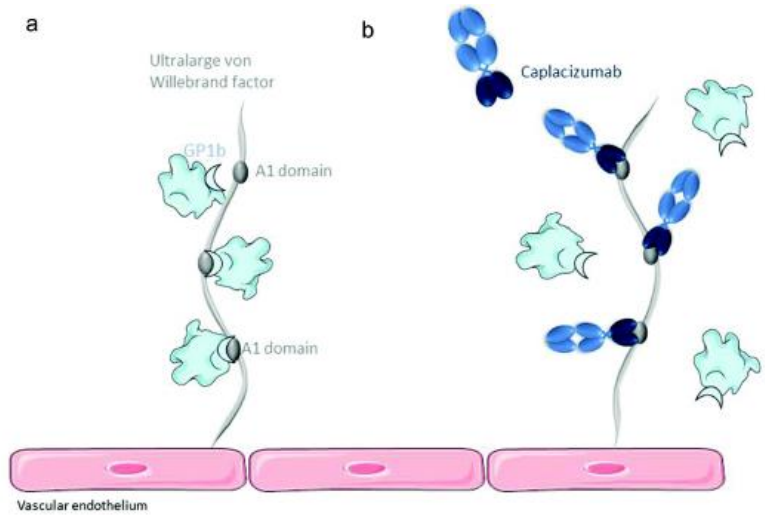


- Without preemptive treatment: 17/23 clinical relapses (74%) (multiple in 11) after a median follow-up of 7 y;
- Cumulative incidence of relapse: 0.26/y

Caplacizumab: a small antibody with big implications for iTTP

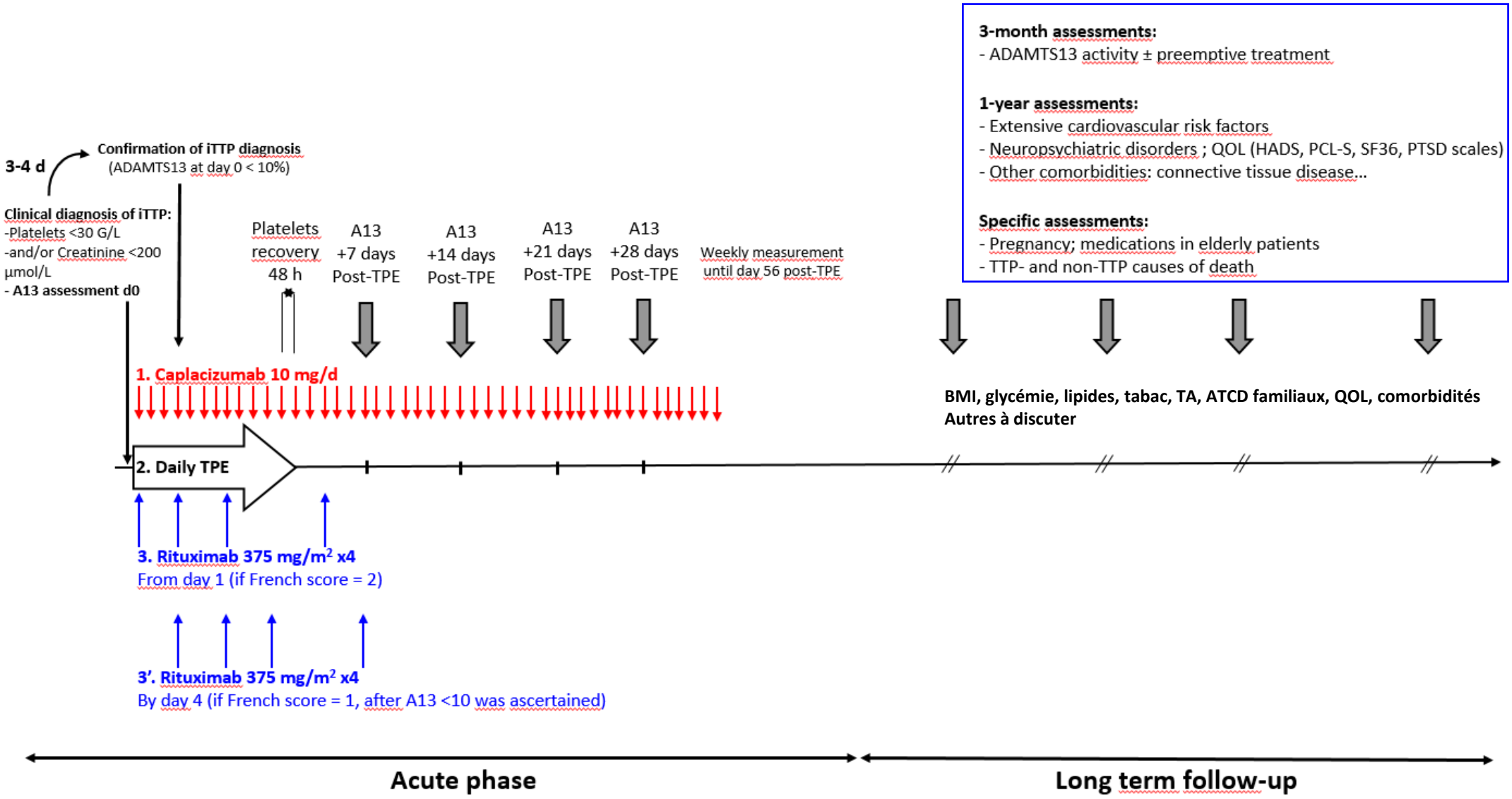


Therapeutic class of proteins derived from the heavy-chain variable domains that occur naturally in heavy-chain Ig from *Camelidae*



Poullin et al., Drugs of Today, 2019

Thérapies ciblées dans le PTT



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

La plasmathérapie reste à ce jour insuffisante

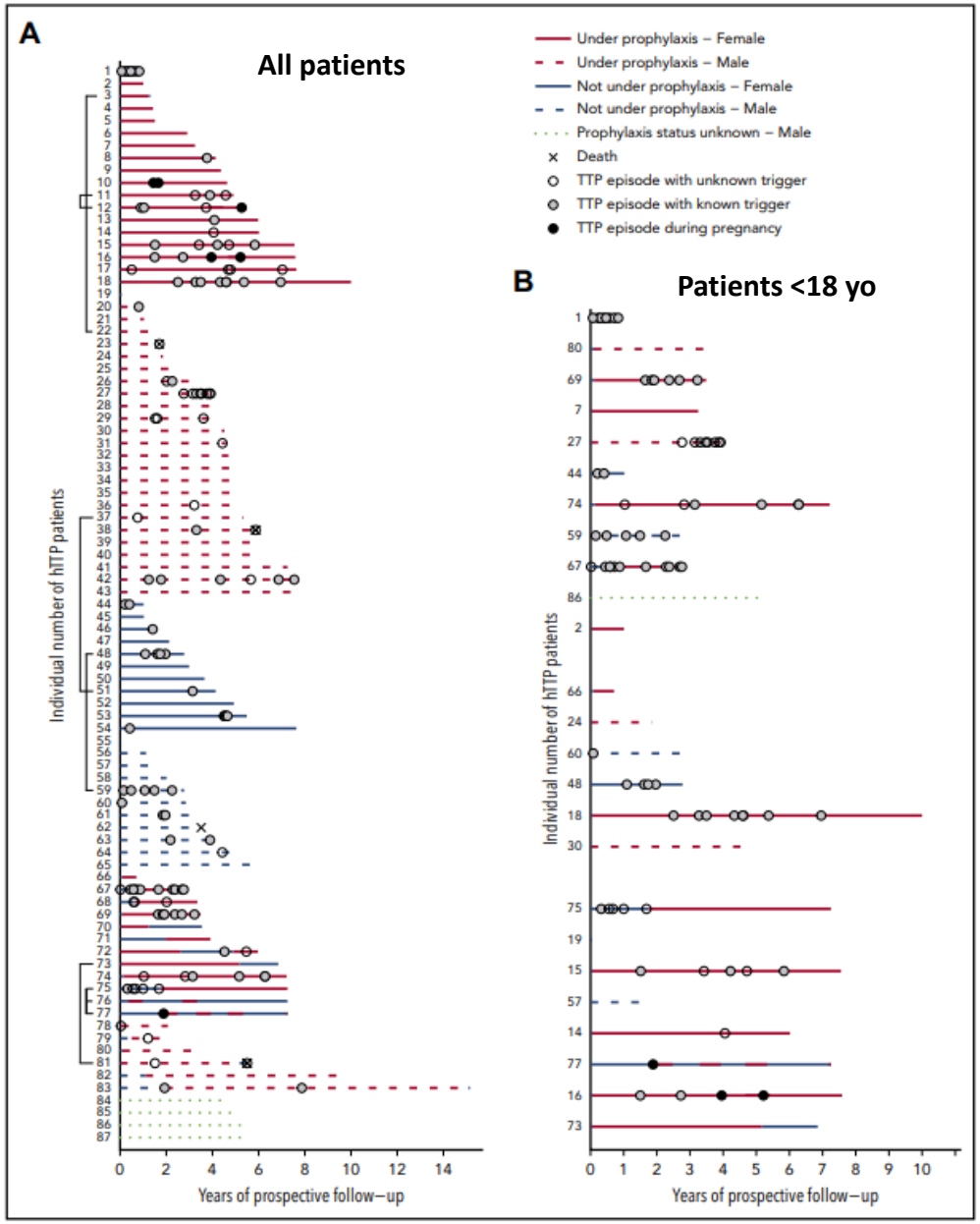


Table I. Comparison of baseline disease activity between the prophylactic FFP and on-demand FFP groups.

	Prophylactic FFP infusion $n = 41$	On-demand FFP infusion $n = 14$	P value
Age	38·6 (30·2–43·8)	19·7 (7·6–38·8)	0·03*
Sex (F/M)	24/17	9/5	0·76†
ADAMTS13 gene mutation			
Homozygote	9	1	0·45†
Compound heterozygote	31	13	
One mutation + SNP	1	0	
Prophylactic FFP infusion			
Dosage of FFP in 1 month (ml)	720 (480–960)	NA	NA
Dosage of FFP per body in 1 month (ml/kg)	13·2 (8·3–19·2)	NA	NA
Treatment periods (year)	17·6 (12·4–28·6)	NA	NA
Baseline laboratory finding			
Platelet count (10^9/l)	138 (65–192)	243 (158–302)	<0·01*
Haemoglobin (g/l)	131 (120–145)	132 (121–144)	0·85*
Lactate dehydrogenase (U/l)	198 (169–262)	193·5 (143–249·8)	0·49*
Serum creatinine (mg/dl)	0·71 (0·6–1·13)	0·58 (0·35–0·73)	<0·01*
Organ damage			
Any organ damage	16	0	0·014†
Renal impairment	13	0	
Cerebral infarction	6	0	
Cardiac hypofunction	1	0	

Registre international + cohorte japonaise

Les épisodes de PTT surviennent (hommes = femmes), chez des patients traités (maladie plus active) ou non traités/à la demande (maladie plus sporadique)

Apports d'ADAMTS13 insuffisants

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

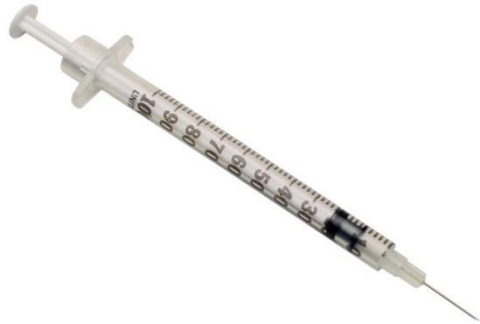
Treatment = plasma infusion

Plasma infusion brings exogenous ADAMTS13 (the missing enzyme)

Cumbersome procedure (needs regular hospitalizations): QOL impacted

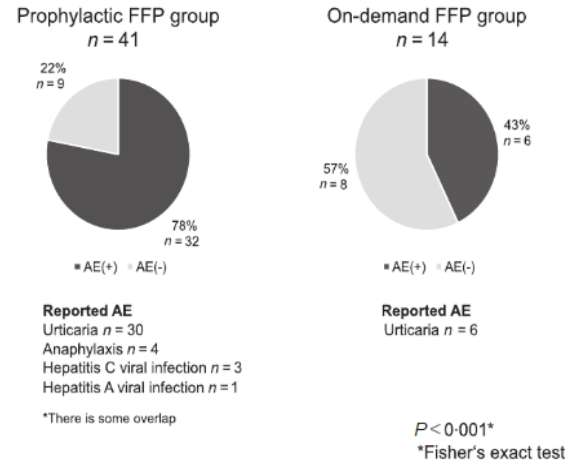
A need to alleviate the current management

vs



Ambulatory care

Side effects:



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

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Takeda Announces Favorable Phase 3 Safety and Efficacy Results of TAK-755 as Compared to Standard of Care in Congenital Thrombotic Thrombocytopenic Purpura (cTTP)

January 5, 2023

- *Results are From First and Only Phase 3 Trial in cTTP, an Ultra-Rare Disease with Limited Treatment Options*
- *cTTP is Caused by a Deficiency in ADAMTS13 Protease;[1] TAK-755 Is Designed to Replace Missing or Deficient ADAMTS13 Enzyme[2]*
- *Takeda Plans to Seek Marketing Authorization for TAK-755 as the First ADAMTS13 Replacement Therapy for the Treatment of cTTP*

Réduction de la survenue de thrombopénies de 60%

Actuellement:

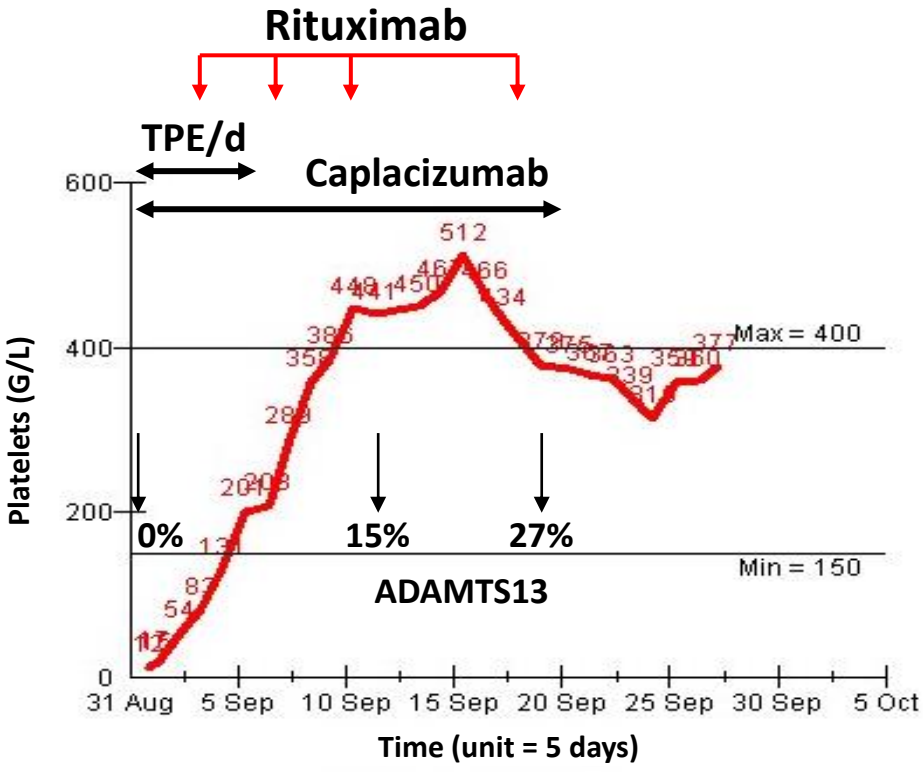
- Accès compassionnel dérogatoire pour les patients mal contrôlés/intolérants au plasma

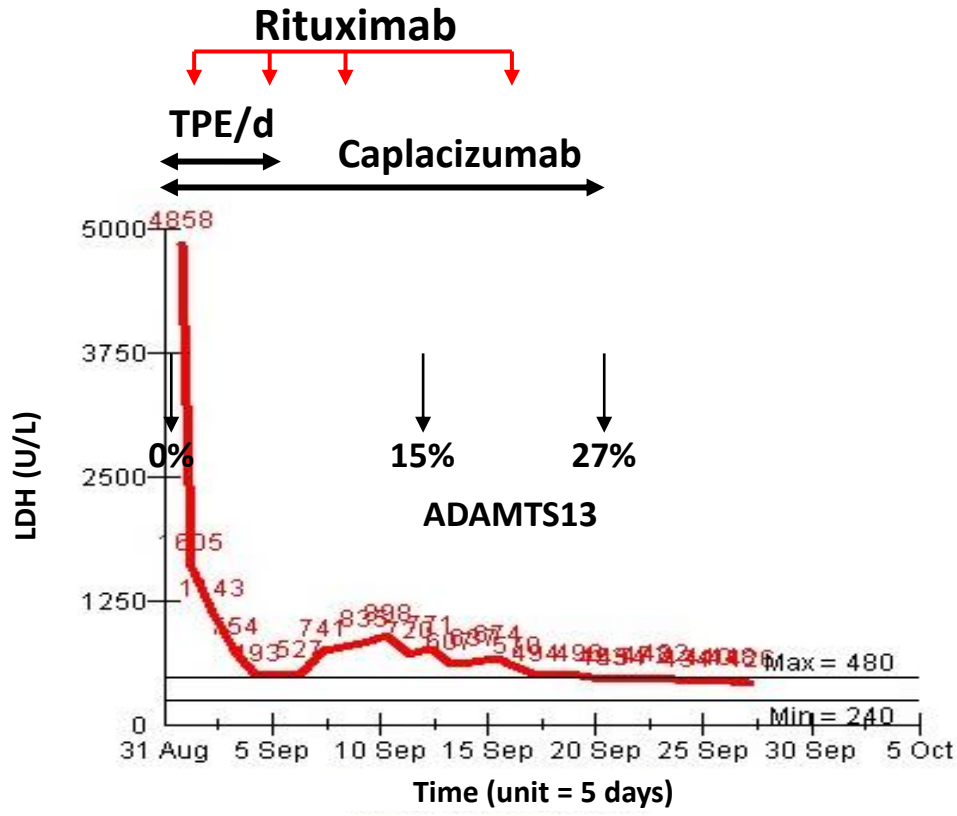
- Programme d'accès précoce en cours (début 2024 ?)

- 3 patients actuellement en France (52 dans le monde; 16 enfants)

Retour en 2023…

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



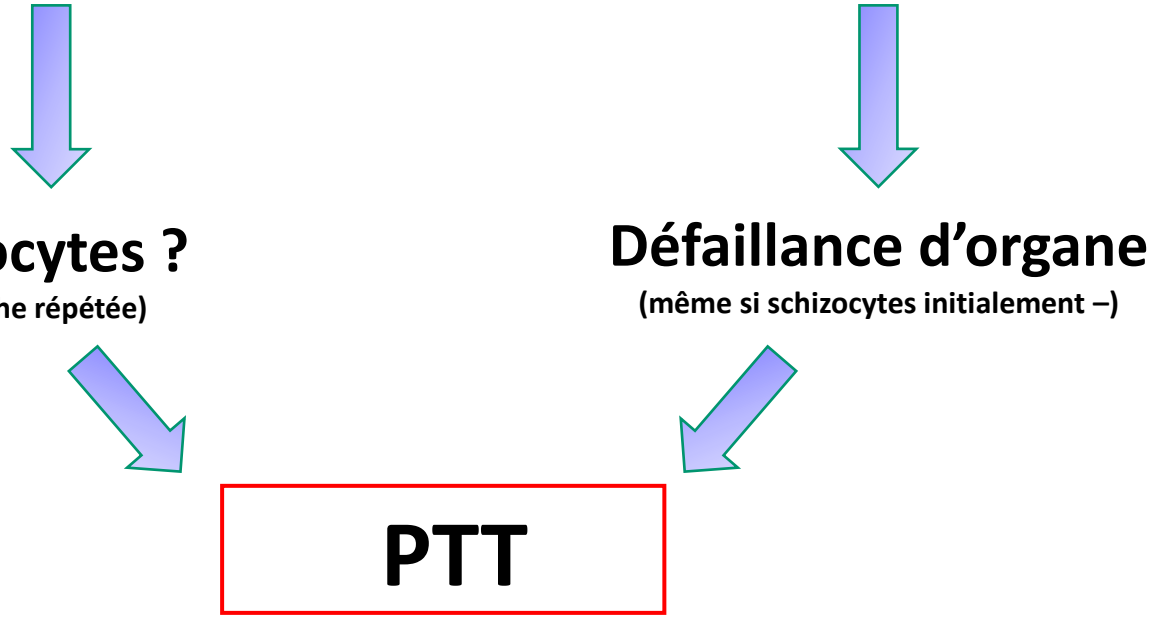


< 7 days of TPE and ICU stay – No exacerbation – Caplacizumab stopped when A13 > 20%
Caplacizumab could negativate the worse prognosis of cerebral and cardiac involvement

P. Coppo, personal communication

Ce qu'il faut savoir pour sauver un patient atteint de PTT

1. Thrombopénie + Anémie hémolytique mécanique/hémolyse



2. Référer le patient ou contacter une équipe référente

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

Conclusion: 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+++; next step: TAK755 for cTTP

3. Caplacizumab frontline, in association with immunosuppression and TPE, nicely prevents unfavorable outcomes in iTTP

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 (PEX-free) should be evaluated, in the next future

PNDS du CNR-MAT

Protocole National de Diagnostic et de Soins (PNDS)

Le Syndrome Hémolytique et Urémique (SHU)

Centres de Références des Maladies Rénales Rares (SORARE, NEPHROGONES, MARHEA)
et Maladies Rares Immuno-Hématologiques (CNR des microangiopathies thrombotiques)

Sous l'égide des filières ORKiD et MaRIH

Février 2021

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

Le CNR-MAT

Site coordonnateur - 5 sites constitutifs - 21 centres de compétence - 2 laboratoires de référence

Départements d'outremer

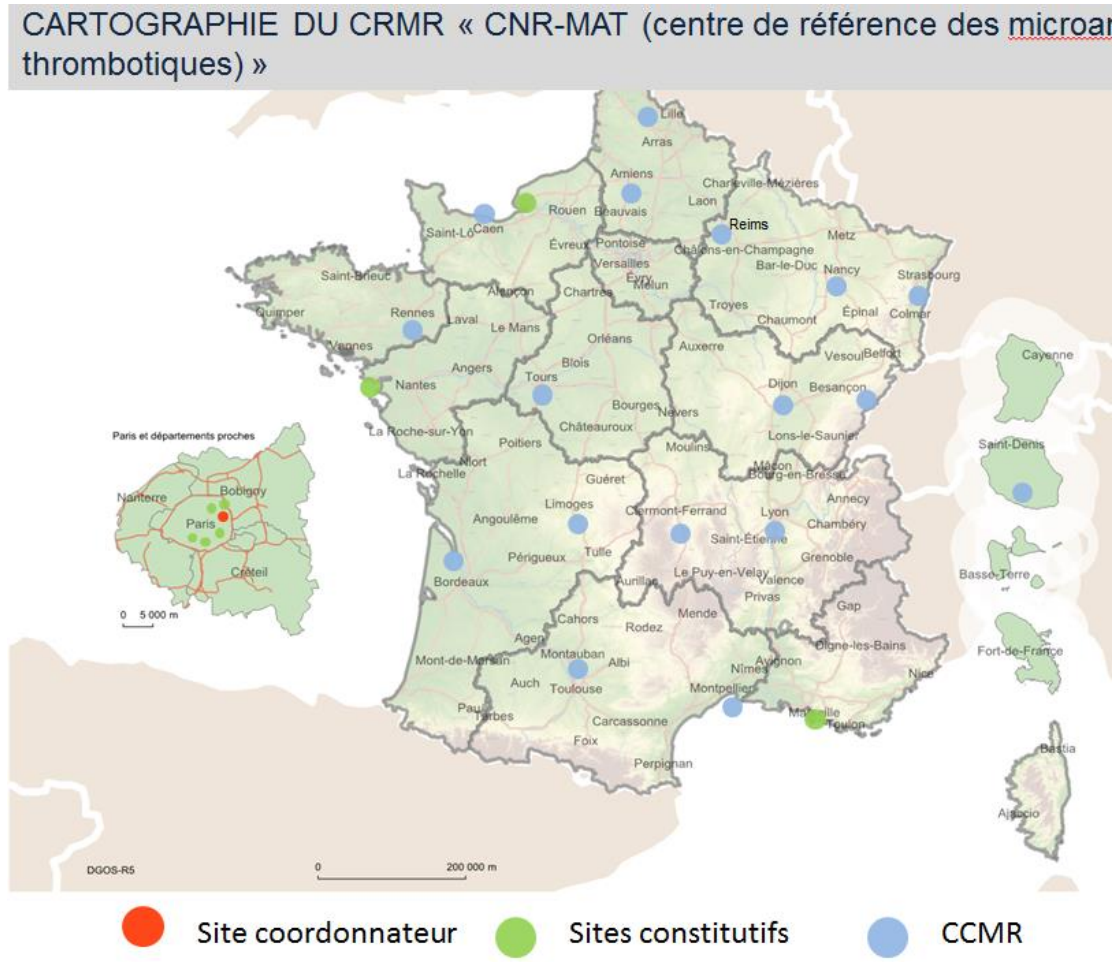
Couverture nationale satisfaisante

Forte participation des centres aux activités du CNR-MAT

Exploration/traitement homogène et précoce des patients

Sites multidisciplinaires+++

Maillage national



The CNR-MAT

Consortium PROFILE & TOLERATE (H2020)

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

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

TOLERATE