

Nouveautés dans les MAT



Journée MaRIH
Océan Indien

Paul Coppo
paul.coppo@aphp.fr

AP-HP et Sorbonne Université



Centre de Référence des Microangiopathies Thrombotiques



Journée régionale MARIH Océan indien – Octobre 2019

MAT = un syndrome

- Anémie hémolytique mécanique
- Thrombopénie périphérique
- Défaillances d'organe de sévérité variable

PTT

- Héréditaires
- Acquis

1-4 cas / million hab /an

25% des MAT

SHU

- STEC+, infection
 <1 cas / 10^5 hab /an
- Lié au complément

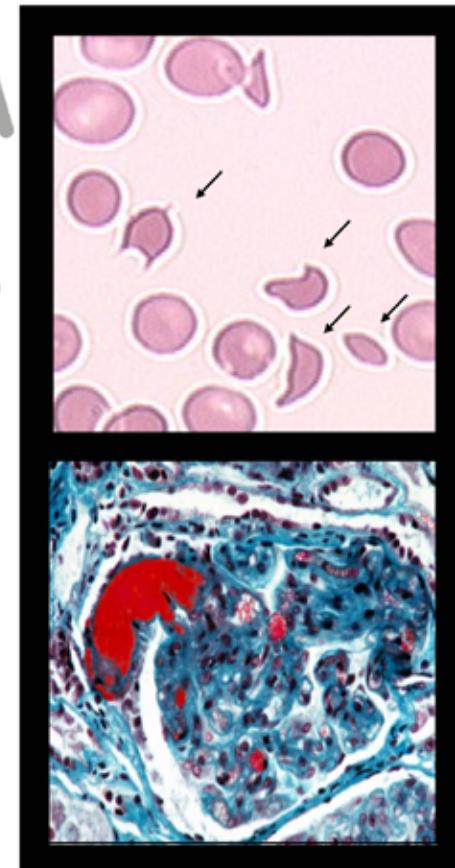
2-4 cas / million hab /an

20% des MAT

Autres entités

- HELLP Sd
- CAPS
- HTA malignes
- Cancers
- Transplantation

> 50% des MAT



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TTP: definition

E. Moschcowitz, 1924

- Microangiopathic hemolytic anemia
- Profound peripheral thrombocytopenia ($< 30 \text{ G/L}$)
- Organ failure of variable severity
- Severe ADAMTS13 deficiency

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Congenital

(Upshaw-Schulman syndrome)

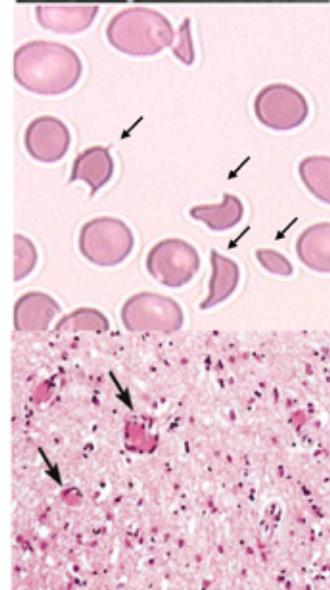
Neonatal/post neonatal period
Childbearing age women

Immune-mediated

Women, 20-50 yo

2-3 cases / $10^6 \text{ hab} / \text{y}$

$< 0.13 \text{ cases} / 10^6 \text{ hab} / \text{y}$



iTTP: clinical presentation

	<i>CNR-MAT, 2010 (N = 160)</i>	<i>Kremer Hovinga et al. 2010 (N = 60)</i>	<i>Veyradier, 2001 (N = 66)</i>
Age (y)	39.9±15	41 (9 – 72)	-
Weight (kg)	69.5±18.6	-	-
Africans-Carribbeans-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 ($\times 10^9$ /L)	20.4 ± 19.2	11 (2 – 101)	35 ± 27
Creatinine ($\mu\text{mol}/\text{L}$)	127 ± 106	141 (61 – 581)	162 ± 140
ANA	53%	-	-
ESRD	0	-	1

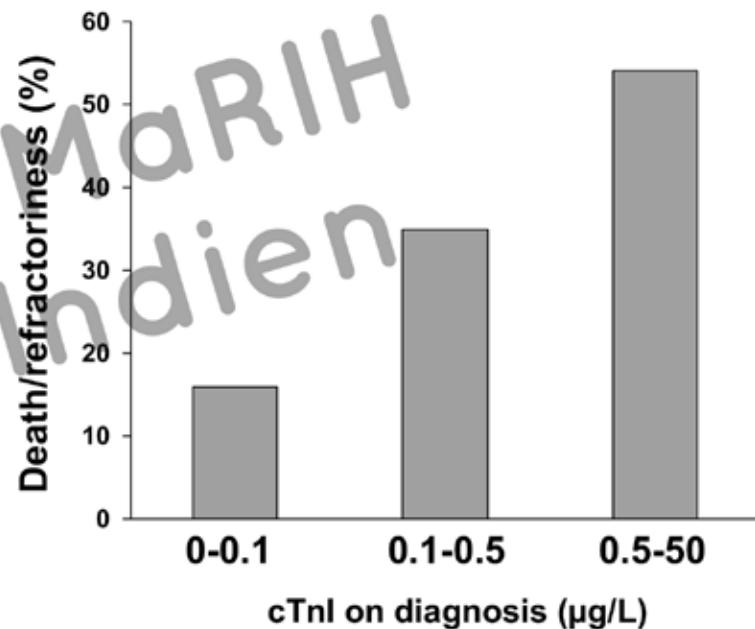
Prognostic value of cardiac troponin I (cTnI)

133 patients – Acquired idiopathic TTP (ADAMTS13 < 10%; Abs +)

cTnI: independent factor for death/refractoriness

	Odds ratio	95%CI	P-value
cTnI >0.25 µg/L	2.86	[1.13,7.22]	0.024
Age (y) ≤40	1		0.7
[41,60]	1.54	[0.49,4.87]	
>60	1.76	[0.48,6.54]	
Neurologic involvement	1.66	[0.58,4.78]	0.4
eGFR	0.61	[0.23,1.63]	0.32

Higher levels = worse outcome



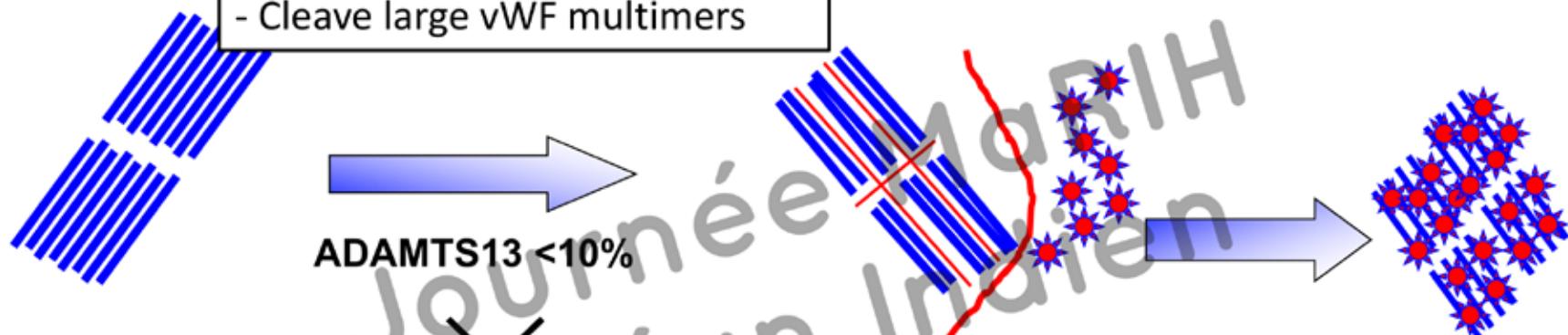
Reliable marker of severe disease
(better than others: age, CNS involvement, very high LDH level, renal failure)

Pathophysiological basis of TTP treatment

1. Replenish ADAMTS13 levels:

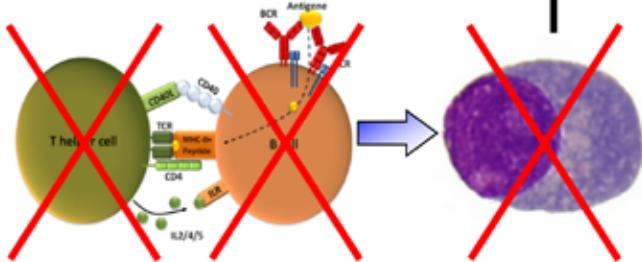
- Saturate anti-A13 Abs
- Cleave large vWF multimers

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



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 TTP

Vol. 325 No. 6

PLASMA EXCHANGE VS. PLASMA INFUSION FOR TTP — ROCK ET AL.

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THE NEW ENGLAND JOURNAL OF MEDICINE

Aug. 8, 1991

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*

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.

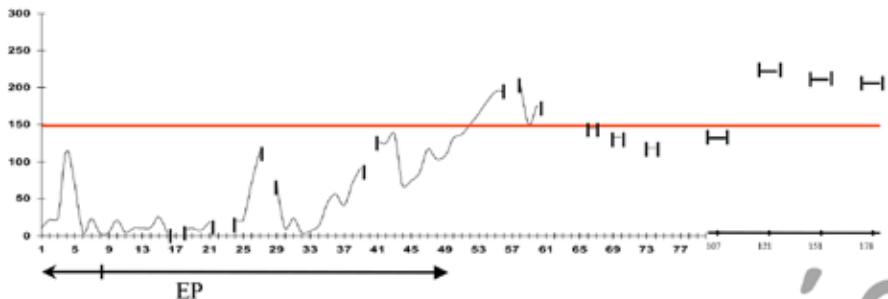
**Daily therapeutic plasma exchange + steroids in emergency until remission
= core treatment of TTP**

With this regimen, prognosis was outstandingly improved

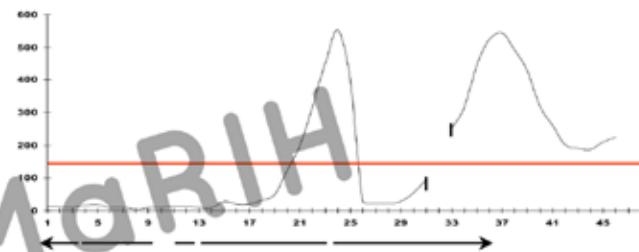
Remission/survival is currently of **85%**, vs almost 0% before

Unmet needs with standard treatment I.

Exacerbations (~ 50% of patients)



Refractoriness (~ 10% of patients)



Patients with a suboptimal response to standard treatment

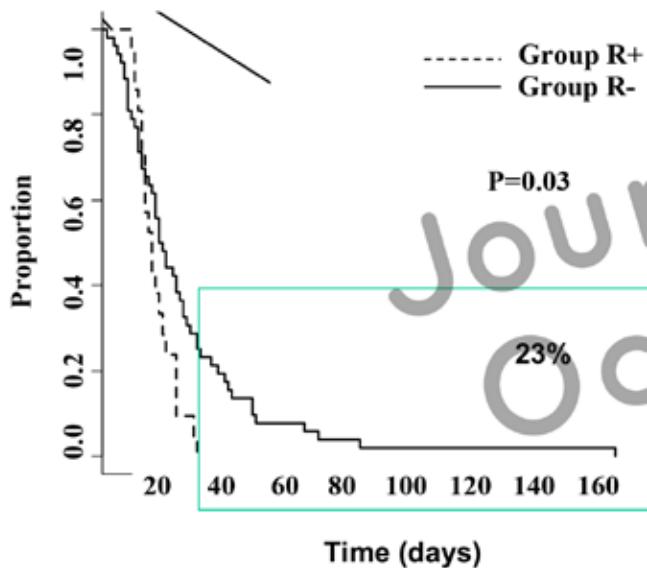
Exposed to a higher risk of death

TPE-related complications
(28% of cases)

How to improve these results?

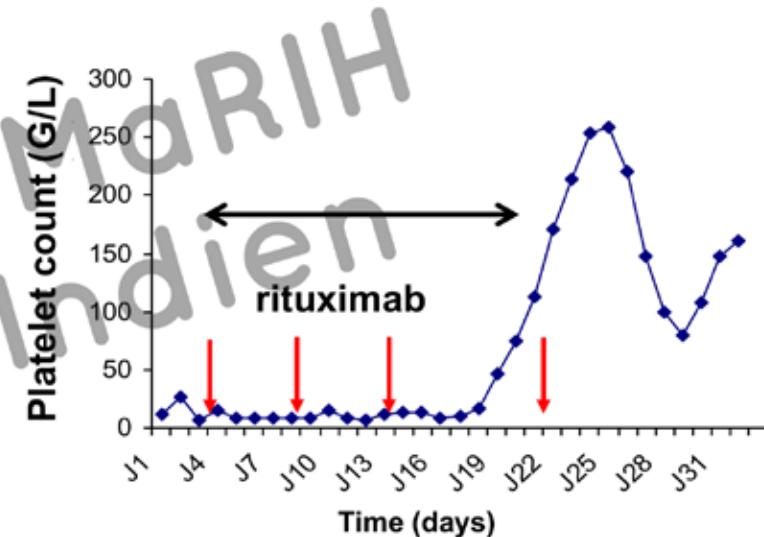
Rituximab in acute TTP with suboptimal response

Rituximab prevents long term responses to TPE



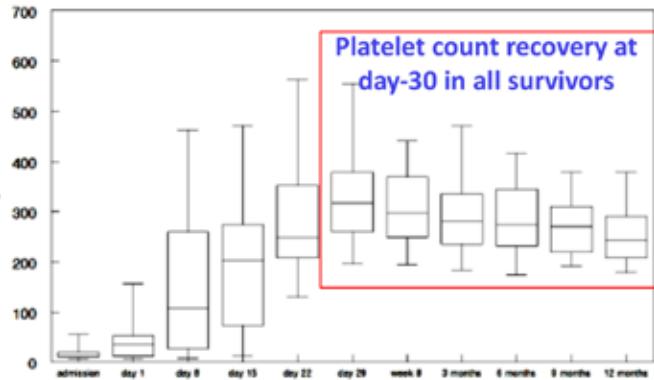
Rituximab limits the duration of TPE treatment

Rituximab is not efficient in real time

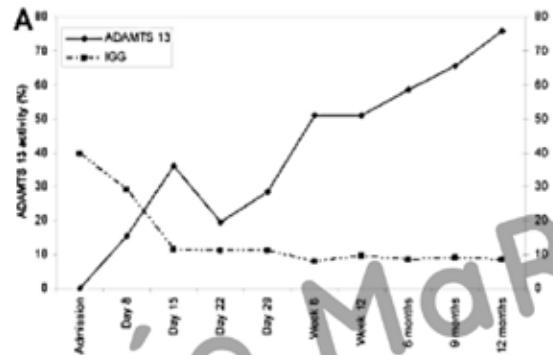


Mean time to platelet count recovery after the first rituximab infusion: 12 ± 6.7 d

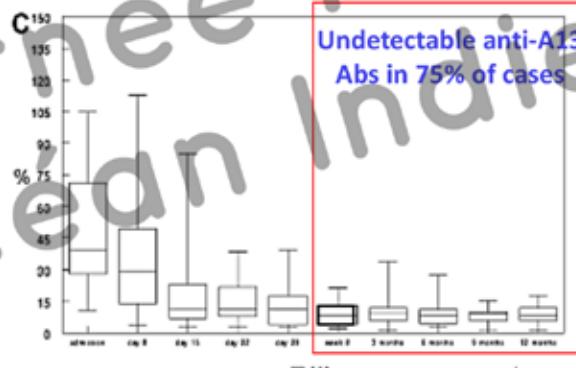
Rituximab in association with TPE as a first line therapy in TTP



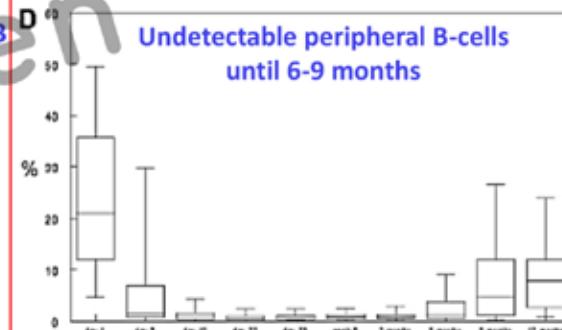
Platelet count recovery at day-30 in all survivors



Detectable A13 activity 75% of cases



Undetectable anti-A13 Abs in 75% of cases



Undetectable peripheral B-cells until 6-9 months

Median time to sustained platelet count normalization = 12 d

Inpatient stay is significantly reduced

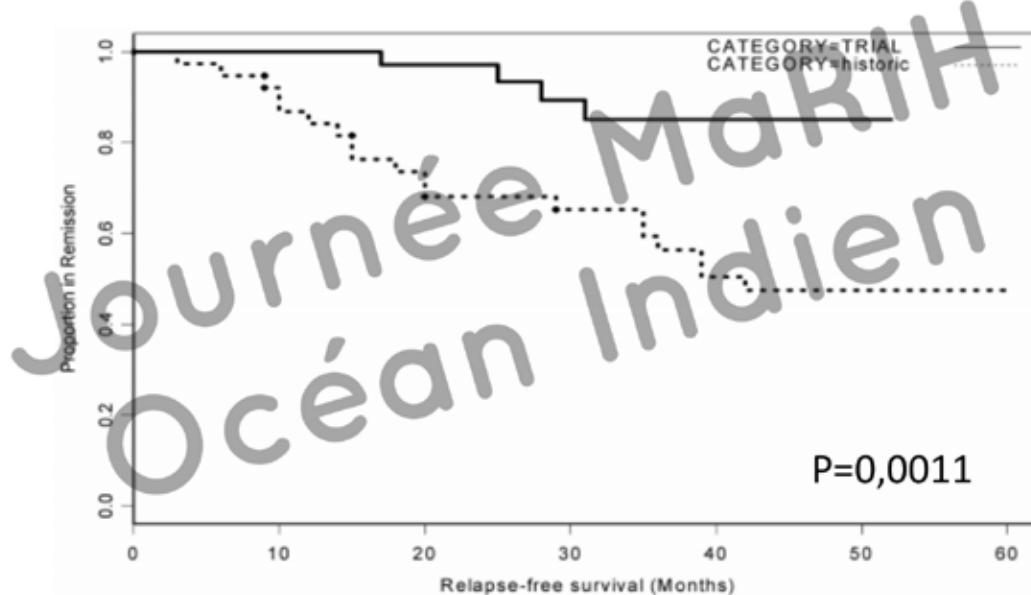
However, some early deaths occurred... rituximab is not efficient immediately

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

Should all patients receive rituximab front-line???

Scully et al., Blood 2011

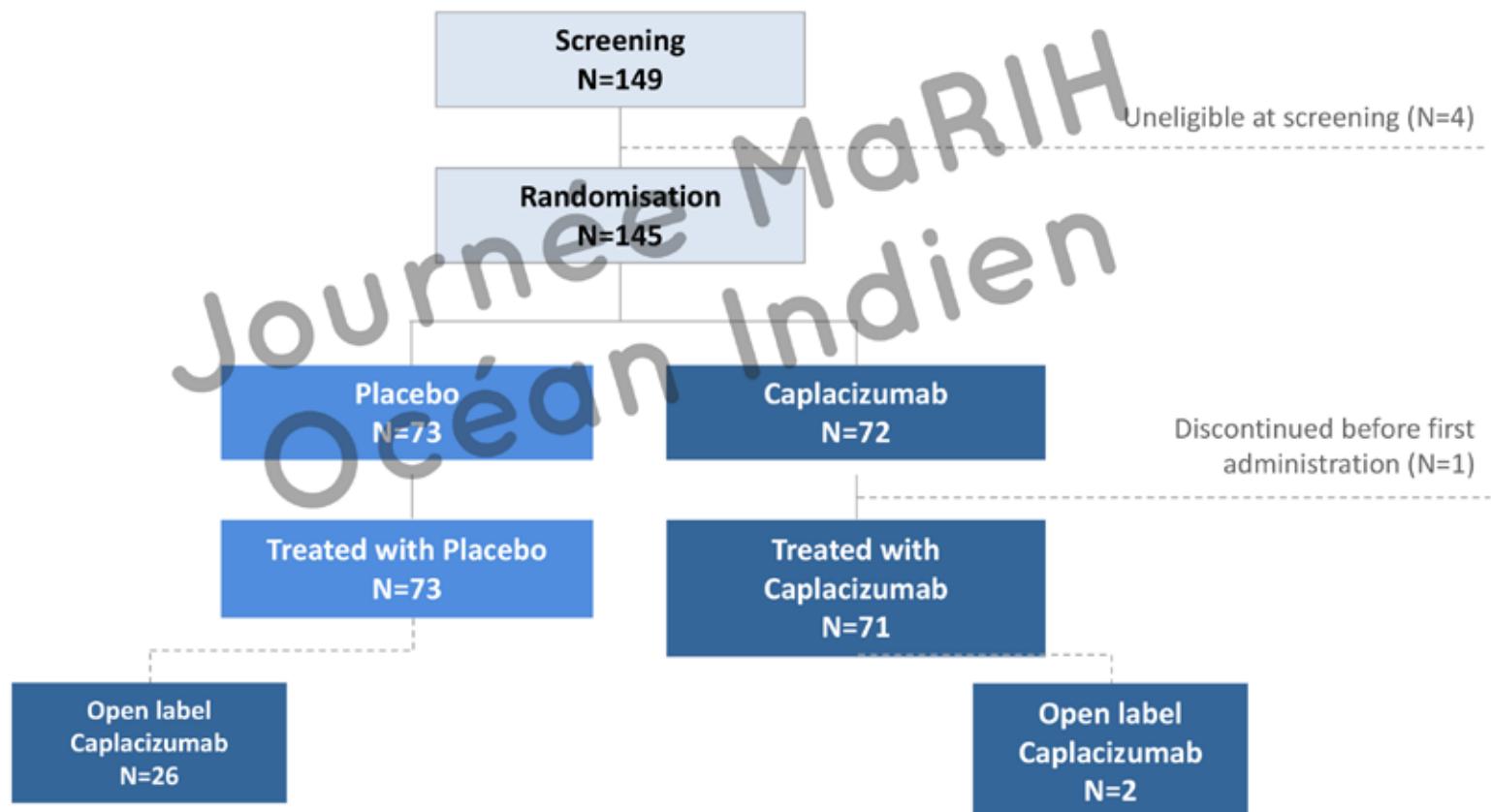
Risk of overtreatment for a significant nb of patients at the acute phase..... but patients are remarkably protected from relapses for 12-18 months



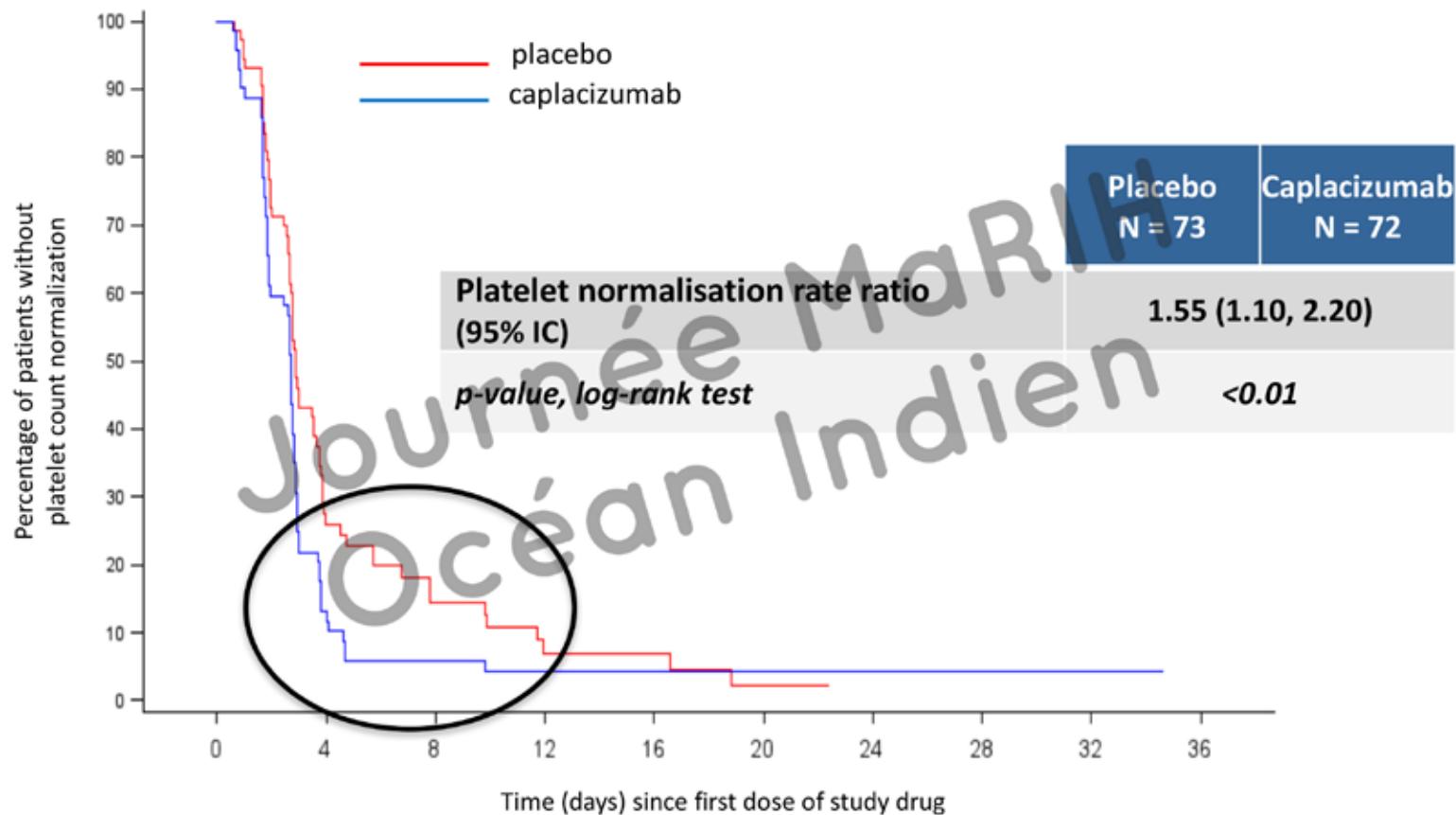
As 40% of patients remain with an undetectable (<10%) ADAMTS13 activity after the acute phase, and other 40% remain with a decreased (10-50%) activity, the number of patients needed to treat to normalize ADAMTS13 activity is $5/4 * 0.85 = 1.5$ (15/10; in 5: rituximab useless or inefficient)

A new player in the game: the anti-vWF nanobody caplacizumab

TITAN and HERCULES trials



Primary endpoint: time to platelet count recovery*



* Platelet count response was defined as initial platelet count $\geq 150 \times 10^9/L$ with subsequent stop of daily PE within 5 days

2nd key secondary endpoints

Number of patients (%)	Placebo N=73	Caplacizumab N=72*
Total number of subjects with at least one of the events	36 (49.3)	9 (12.7)
aTTP-related death ²	3 (4.1)	0
Exacerbation of aTTP episode ³	<u>28 (38.4)</u>	<u>3 (4.2)</u>
at least one treatment emergent major thromboembolic event:	6 (8.2)	6 (8.5)
p-value		<0.0001

Efficacy on exacerbations suggests early efficacy

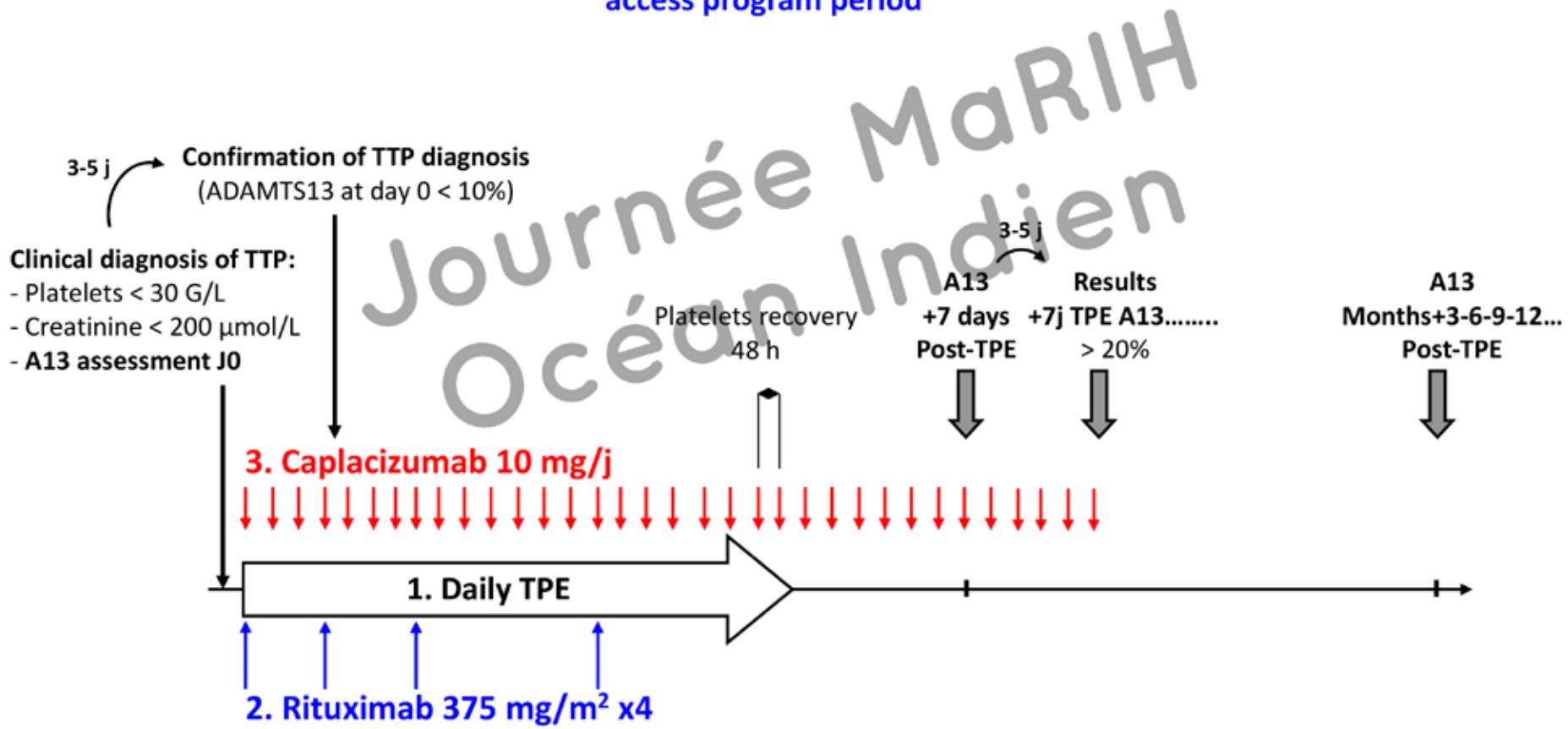
Caplacizumab should protect patients until B-cell depleting therapies improve ADAMTS13 activity

Manageable AE in clinical trials (more epistaxis and gingival bleeding)

After the Greek epic: the « Caplavie » regimen

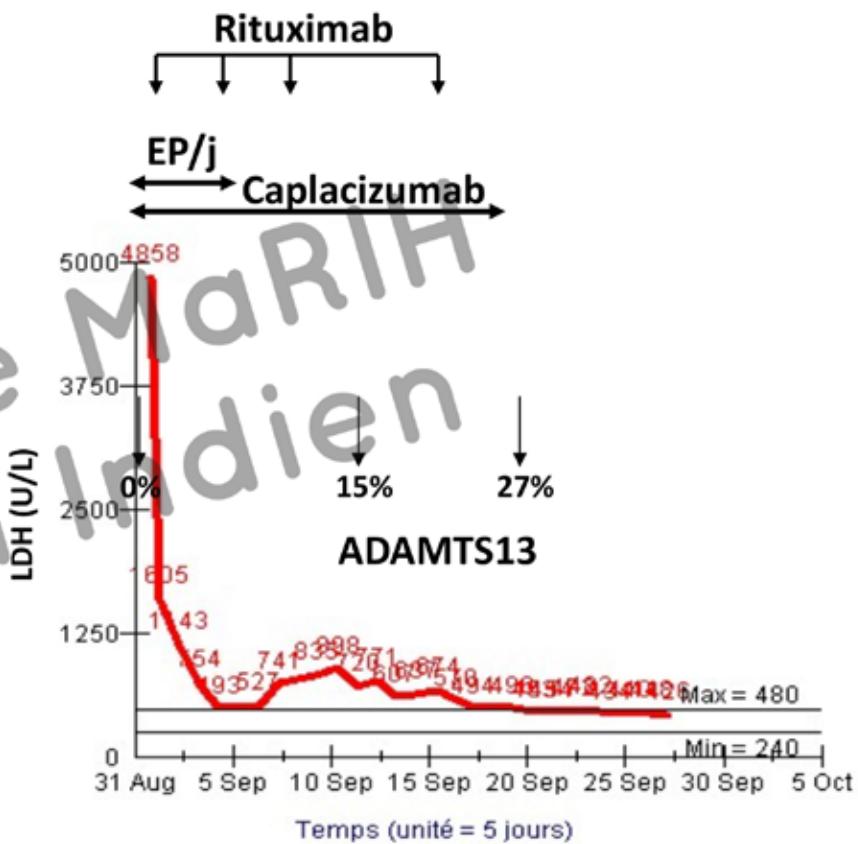
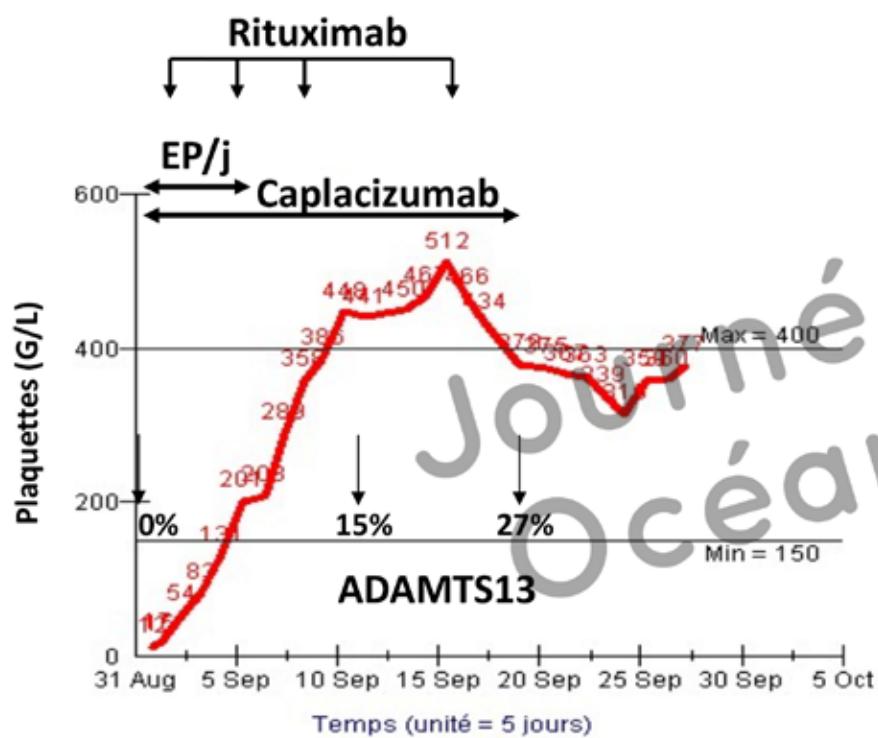
Triplet TPE – Corticosteroids/Rituximab - Caplacizumab

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



Patiente VER... MH

Femme 45 ans – SNC+ - Cœur+ - French Score = 2



< 7 jours d'EP et de séjour en USI – Pas d'exacerbation – Arrêt du capla quand A13 > 20% à J15 du dernier EP

A new hope: the recombinant ADAMTS13?

- Phase 1 multicenter, open-label, dose-escalation clinical study in 15 patients with severe hereditary ADAMTS13 deficiency (concluded 2016)
- Objectives
 - Safety and immunogenicity
 - Pharmacokinetics
- 3 rADAMTS13 (BAX 930) dose cohorts were defined: 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 cTPP 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

**Pourquoi les patients atteints de
PTT meurent-ils encore...?**

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Mrs F... D..., 45 yo

Feb, 15th, in the evening : nausea + 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 TTP made post-mortem; ADAMTS13 on an aliquot of serum <10%...

Mrs M... O..., 39 yo

Chronic thrombocytopenia from childhood; no precise etiology, not exhaustively explored. Exsanguinous-transfusion at day-1 of life for jaundice,

Annual follow-up of platelet count; between 50 and 100 G/L.

Received IVIg + steroids during her 2 pregnancies; thrombocytopenia 5 G/L but were otherwise uneventful,

September, 2014 : increase in serum creatinine level: 112 µmol/l (1.27 mg/dl),

December, 2014 : consults with a nephrologist (hapto<0.3 g/l ; LDH 1.5 N; proteinuria 0.62 g/d)

April, 1st, 2015 : renal biopsy: glomerular lesions consistent with a TMA, **diagnosis of aHUS** retained; TMA work-up made; eculizumab started...

ADAMTS13 activity <5%; anti-A13 Abs negative, hospitalized on April, 13th 2015 for TPE; immediate response. Congenital TTP. Plasma prophylaxis= creatinine/platelets N !

Learning by experience can be painful...

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

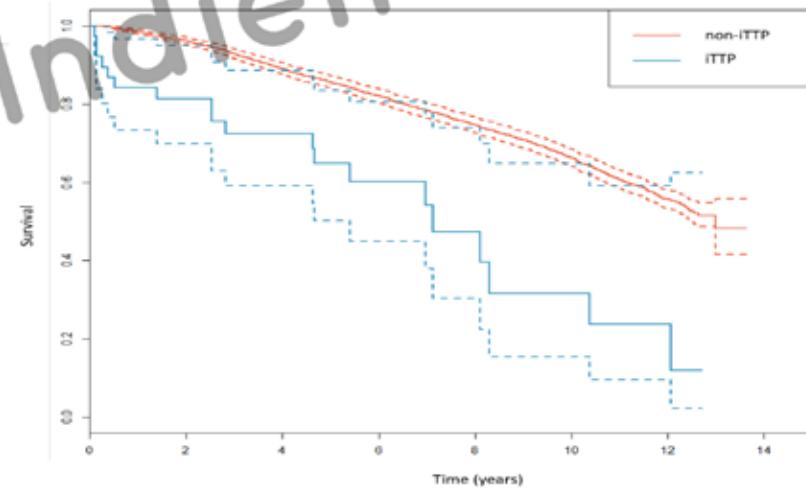
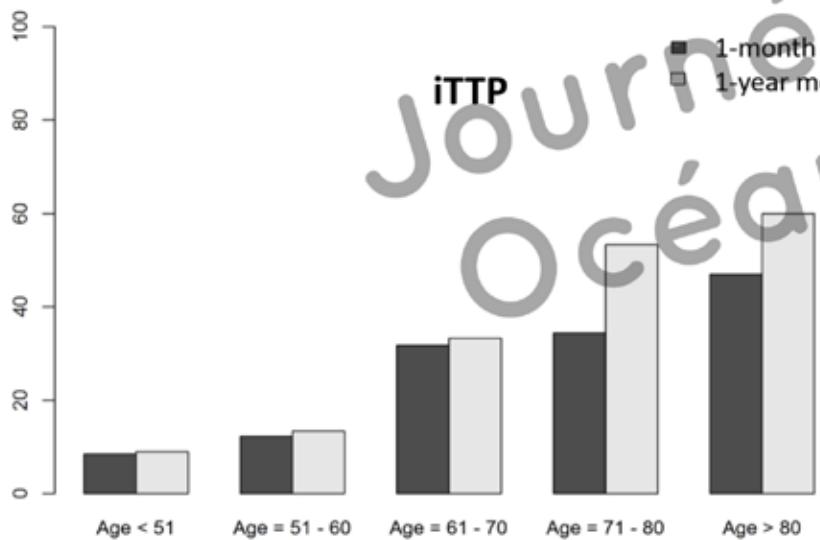
To make clinicians aware of TTP diagnosis remains one of the most important issues

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

iTTP in the elderly: how to raise the bar?

Prevel et al., Blood 2019

	Age < 60 n = 340	Age ≥ 60 n = 71	p-value
Delirium	61 18 %	21 30 %	0.034
Seizures	25 7 %	11 15 %	0.038
Behaviour abnormalities	46 14 %	17 24 %	0.045
Plasma creatinine ($\mu\text{mol/L}$)	89 [73;120]	124 [89;198]	<0.0001
Platelets count (G/L)	13 [9;21]	22 [9;57]	0.002
Haemoglobin level (g/dL)	8 [7;10]	9 [8;11]	0.0007
High French score predictive of a severe ADAMTS13 deficiency (score=2)	273 80 %	43 61 %	<0.0001
Time from hospital admission to diagnosis (days)	1 [1;3]	3 [1;7]	0.0001

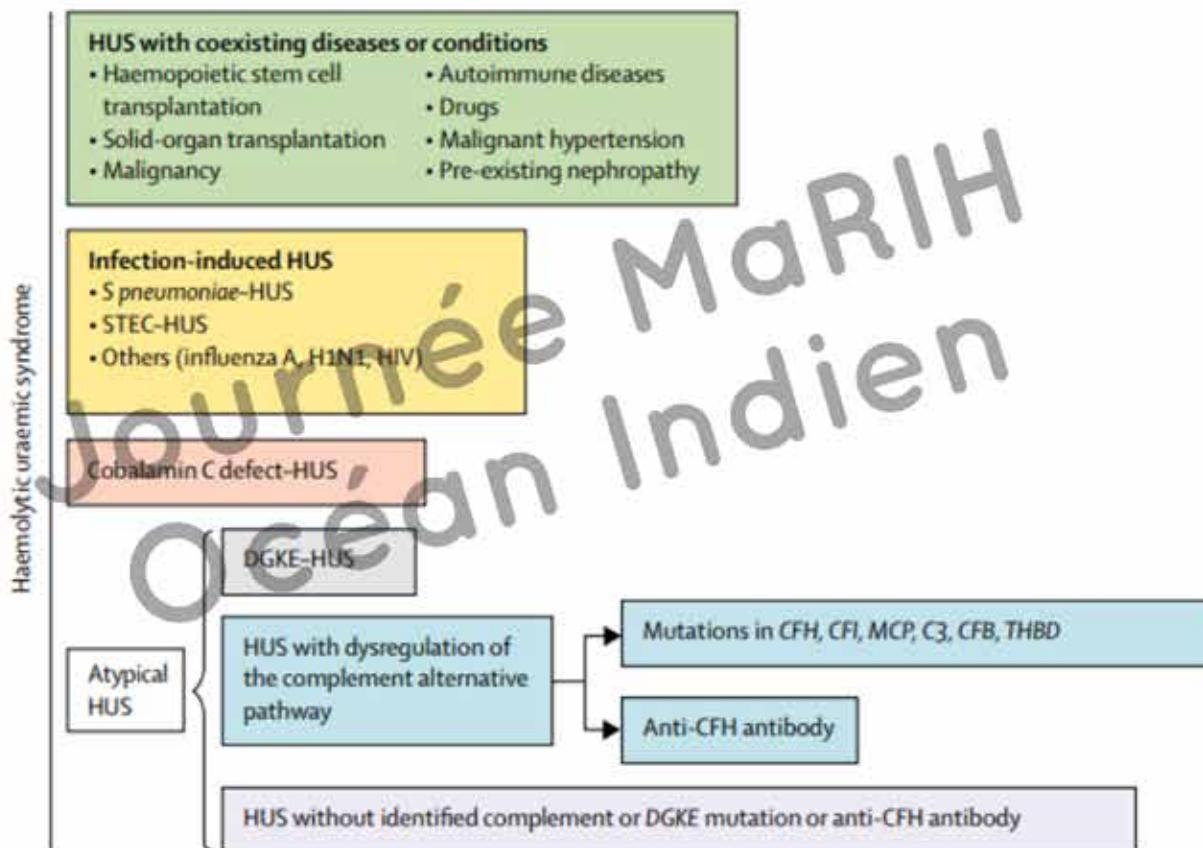


iTTP in older patients has atypical clinical features that may not be alarming at this age but delaying diagnosis, with higher 1-month and 1-year mortality rates; it also negatively impacts life expectancy in survivors

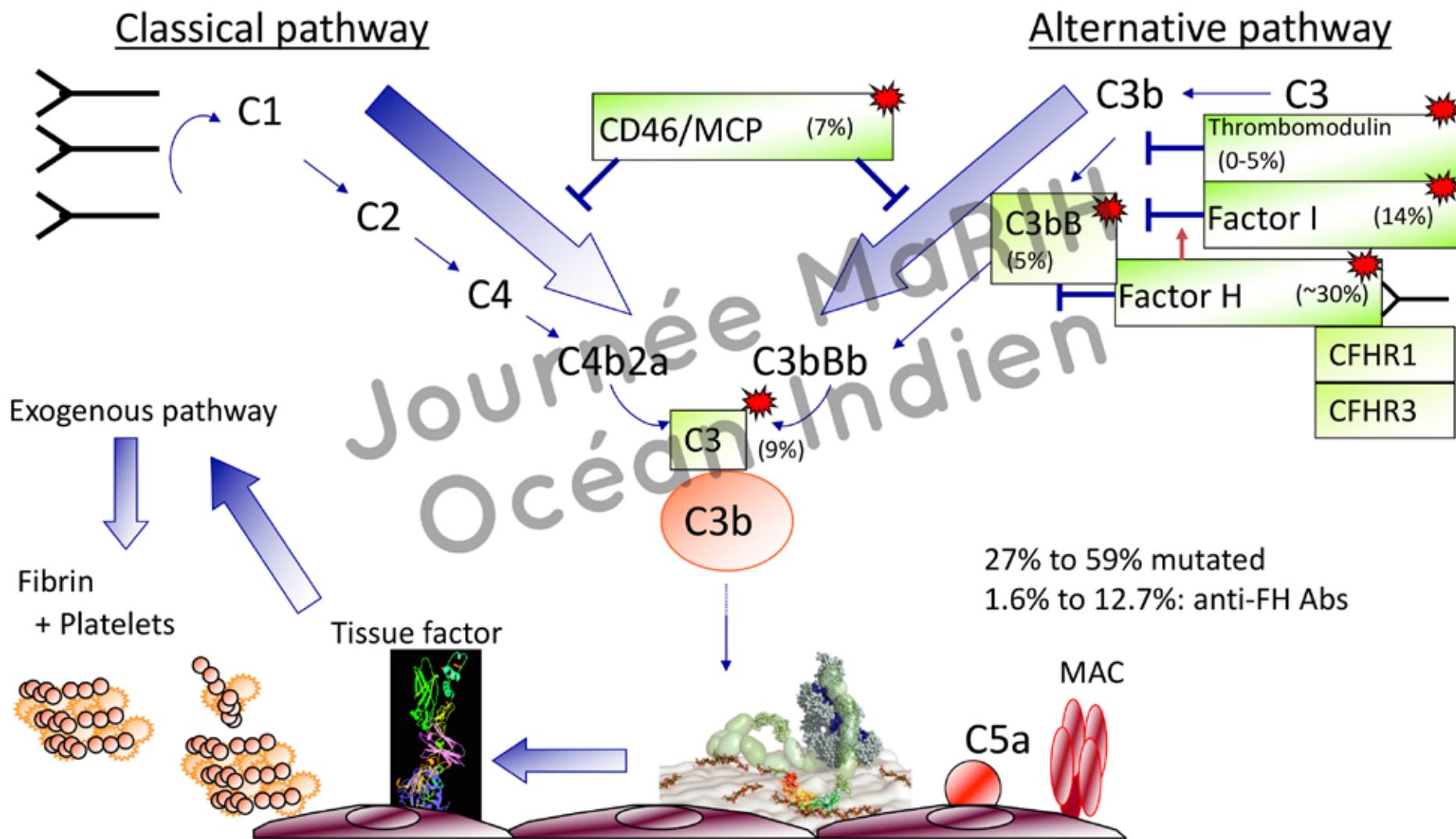
SHU

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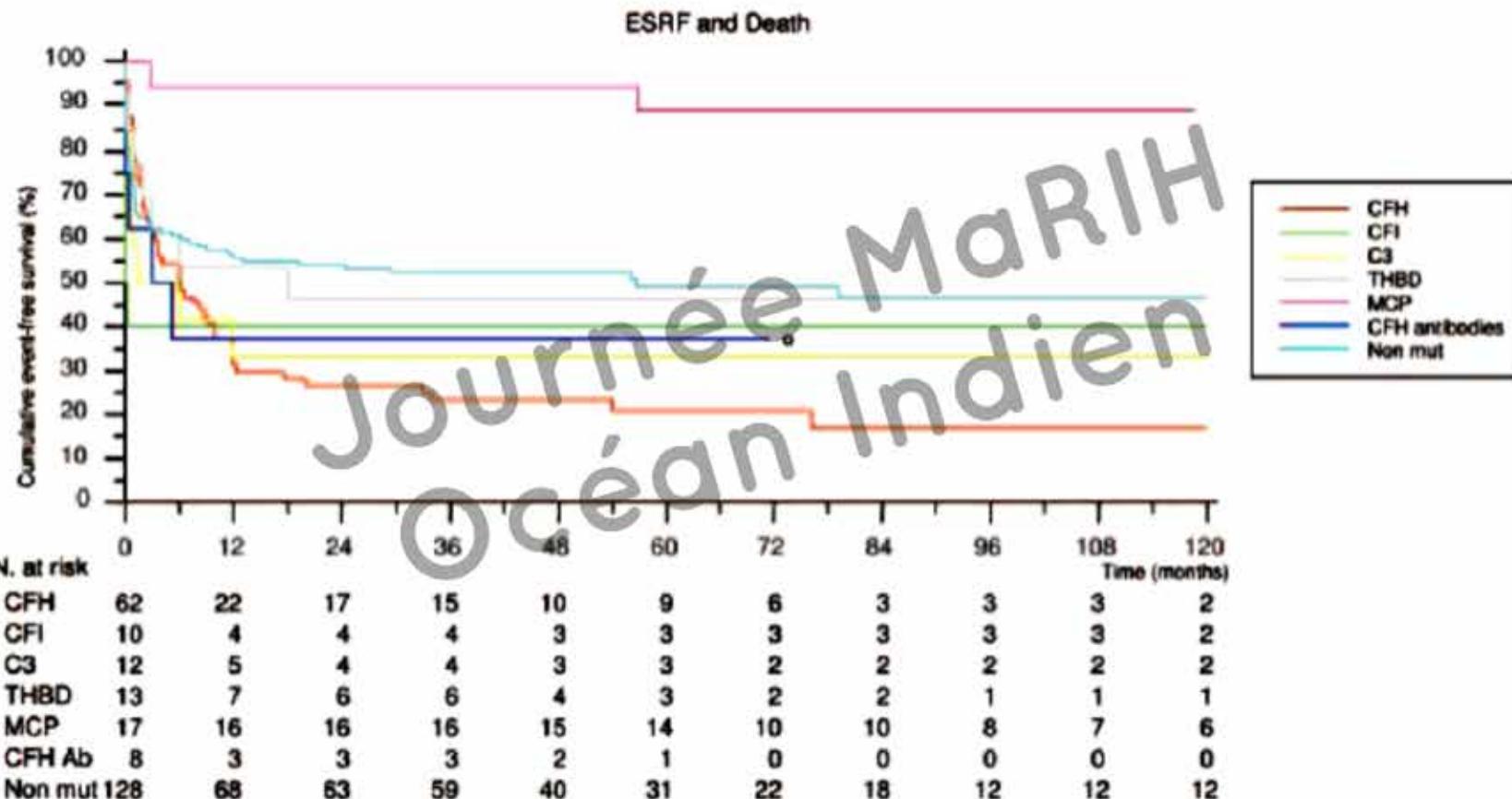
Causes of HUS



Complement-associated HUS



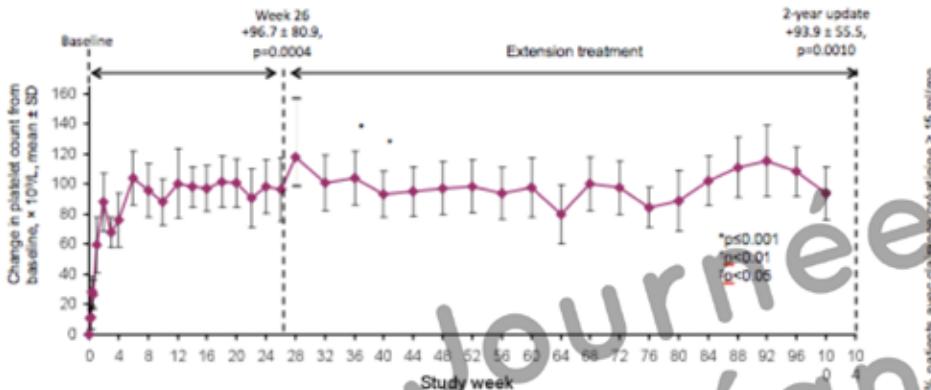
Conséquences cliniques des anomalies du complément



Efficacité d'une stratégie de blocage du complément

Eculizumab continued to inhibit TMA at 2-year update as measured by increased platelet count

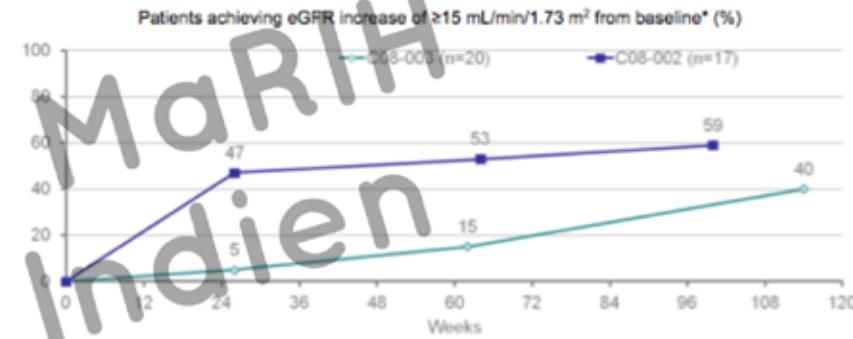
- Primary endpoint of C08-002: mean change in platelet count from baseline through median of 100 weeks of eculizumab



- Platelet normalisation ($\geq 150 \times 10^3/L$) was achieved by 26 weeks in 13/15 patients (87%), who had low platelets at baseline, and was maintained through a median duration of 100 weeks in 12/15 patients

Increasing proportion of patients achieving significant increase in eGFR with long-term eculizumab

- Ongoing renal benefit from baseline observed at 2-year update
 - Continued cumulative increase in percentage of patients achieving a sustained* eGFR increase of $\geq 15 \text{ mL/min}/1.73 \text{ m}^2$ from baseline



Transformation du pronostic vital et d'organe

Réponse hématologique rapide; réponse rénale plus lente, sur le long terme

SHUa dialysé: transplantation rénale sous couvert d'éculizumab

Perspectives d'arrêt (STOPECU: mutation-dépendant)

En cours d'évaluation: forme à demi-vie prolongée (ravulizumab), S/C, autres cibles que le C5...

Drug-associated TMA

Drugs that have been associated with thrombotic microangiopathy (TMA) in the Oklahoma TTP-HUS Registry, 1989–2009.

Mechanism	Number
<i>Acute, immune-mediated</i>	
Quinine	25
<i>Dose-dependent toxicity</i>	
Chemotherapeutic agents	
Mitomycin C	11
Gemcitabine	4
Carmustine	1
Pentostatin, Deoxycoformycin (Nipent®)	1
Calcineurin inhibitor	
Cyclosporine	3
<i>Association with TTP uncertain and pathogenesis unknown</i>	
Alendronate	1
Clopidogrel	1
Cocaine	1
Ticlopidine	2
Trimethoprim-sulfamethoxazole	1
Vancomycin	1

Medina et al., *Curr Op Hematol* 2001

Moll et al., *Am J Kidney Dis* 2001

Eremina et al., *N Engl J Med* 2008

Yui et al., *Am J hematol* 2016

George et al., *Presse Med* 2012

Anti-VEGF agents

Proteasome inhibitors (**carfilzomib**, bortezomib)

Yttrium⁹⁰ (> 200 mCi/m²: associated with renal TMA)

Anti-CD22 immunotoxin (BL22)

Tyrosine kinase inhibitors (imatinib mesylate, dasatinib)

Emicizumab: a new cause of drug-associated TMA

TMAs: conclusion

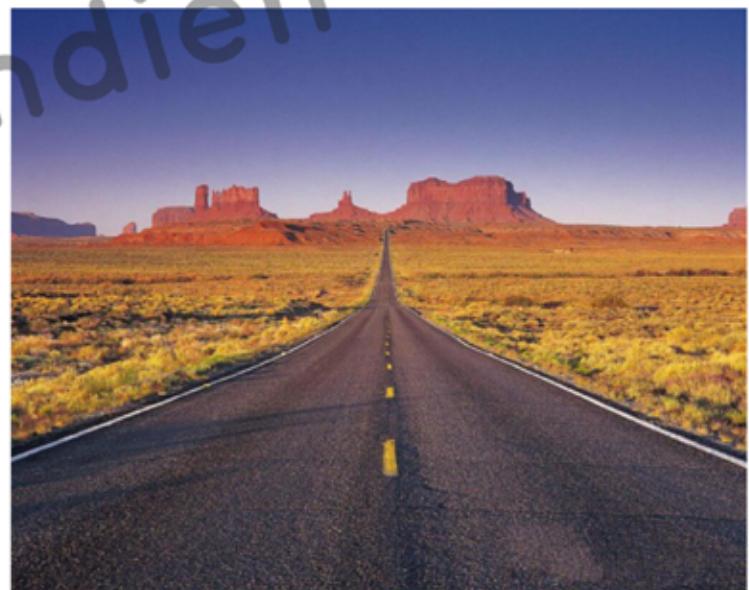
- Les MAT dans leur ensemble ont connu de remarquables progrès dans leur prise en charge et leur pronostic
- Ces progrès sont largement dus à la compréhension des mécanismes physiopathologiques qui les sous-tendent, qui ont permis le développement de thérapies ciblées sur la base d'une classification physiopathologique
- Les autres sources de progrès furent l'établissement de registres et de travaux collaboratifs nationaux ayant permis de réaliser des études cliniques et des essais thérapeutiques, malgré la rareté et l'hétérogénéité de certaines formes; ainsi que l'approche multidisciplinaire de ces pathologies et la mise en commun des expertises



Conclusion

- Axes de travail actuels et à venir:

- poursuite du développement des thérapies ciblées: ADAMTS13 recombinante, anti-FW (caplacizumab) (remplacement des échanges plasmatiques dans un avenir proche ?), anticompléments (formes retard, S/C...), décroissance de la lourdeur de la prise en charge
- optimiser la prise en charge des formes récidivantes (PTT et SHUa: patients jeunes et immunomodulation prolongée; grossesse...)
- Sensibiliser les acteurs au diagnostic des formes rapidement graves (PTT, grossesse++)
- développer l'éducation thérapeutique dans les formes chroniques (PTT, SHUa)
- Concentrer les efforts sur les formes dont le traitement reste insuffisant (MAT + greffe, médicaments)



The CNR-MAT



Consortium PROFILE (H2020)



Filière de santé Maladies Rares Immuno-HématoLOGIQUES



Reconnue par le Ministère de la Santé



Centres de référence maladies rares



Associations de patients



MaRIH
Journées Nationales
de sensibilisation
à la maladie rares
MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

filière de santé
maladies rares

Reconnue par le Ministère de la Santé

Sociétés savantes



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