DOTT.SSA LAURINO MARICA

UO Ematologia e Terapie cellulari - Direttore Dott. E. Angelucci
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Porpora Trombotica Trombocitopenica: ruolo dei nuovi farmaci e collaborazione con il Centro Trasfusionale

Nessun conflitto di interesse

TTP: Definition and clinical presentation

- Microangiopathic hemolytic anemia
- Peripheral thrombocytopenia (<30x10^9/L)
- Organ failure of variable severity (CNS, kidneys, heart, lung…)
- Severe **ADAMTS13 deficiency**

Acquired/Immune (>95%)
Anti ADAMTS13 Antibodies

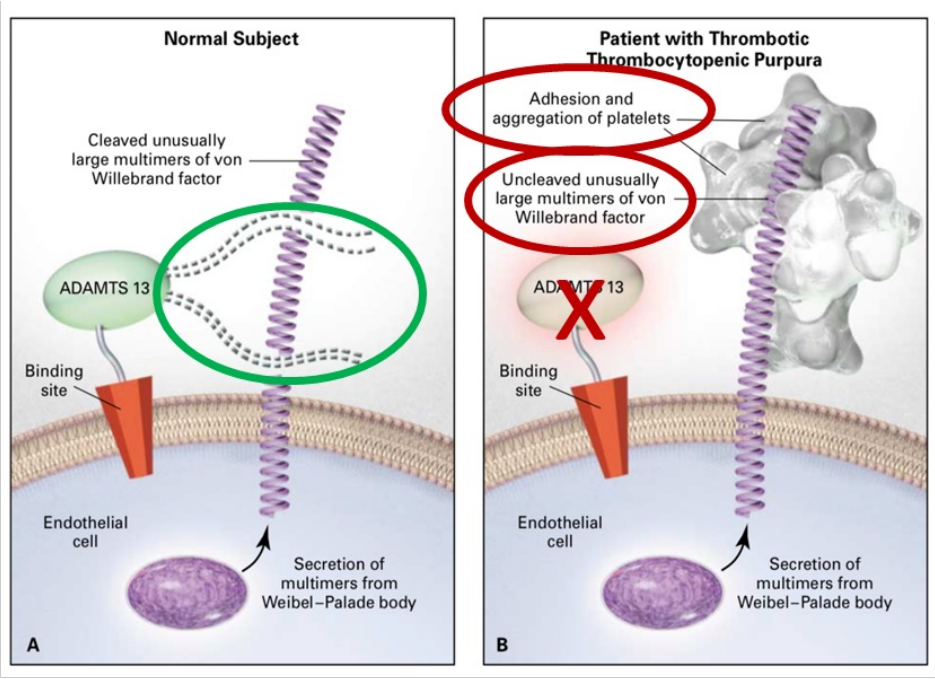
- Acute onset
- Rare 5-11 cases million people year
- M:F ratio 1:3
- Peak of incidence III-IV decades
- Mortality reduced from 90% to 10-20% with appropriate therapy
- Risk of recurrence 30-35%

Congenital (<5%)
(Upshaw-Shulman syndrome).
Homozygous (or double heterozygous) mutation in each copy of the ADAMTS 13 gene (cr. 9q34)

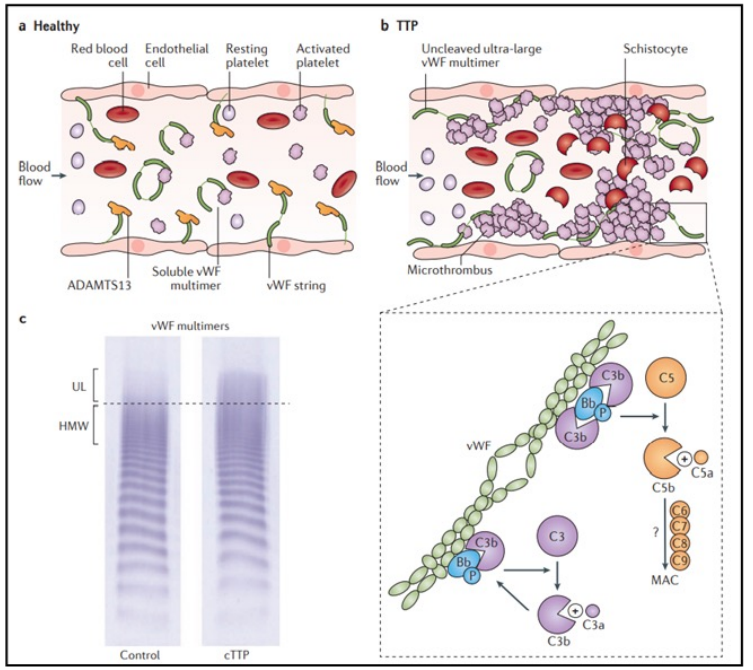
- > 100 mutations
- Unknown prevalence
- M:F ratio 1:3
- Onset within 2 to 5 years or in adulthood (more frequently during pregnancy)

Peyvandi et al Hematologica 2010 – Kremer Hovinga JA et al Nat Rev Dis Primers 2017 – Scully M et al Blood 2014

iTTP: Physiopathology



In normal subjects, ADAMTS 13 (vWF–cleaving metalloprotease) molecules attach to binding sites on endothelial-cell surfaces and cleave unusually large multimers of von Willebrand factor as they are secreted by stimulated endothelial cells. Absent or severely reduced activity of ADAMTS 13 in patients with iTTP prevents timely cleavage of unusually large multimers of vWF. The uncleaved multimers induce the adhesion and aggregation of platelets in flowing blood.



A microvessel in iTTP: excessive microthrombi formation, shear injury to red blood cells flowing through microvessels that are partially occluded by platelet clumps (producing schistocytes and haemolysis) and activation of the **alternative complement pathway on the uncleaved ultra-large vWF strings (inset)**.

Moake JL, NEJM 2002 – Kremer Hovinga JA et al, Nature Rev 2017

iTTP: diagnostic work-up

WORK-UP DIAGNOSTICO SOSPETTA MT
Emocromo
Esame dello striscio periferico per ricerca schistociti (cut-off > 1%)
Test di Coombs diretto
LDH
Dosaggio creatinina
Bilirubina totale + diretta
Dosaggio aptoglobina
PT, aPTT, fibrinogeno, D-Dimero
Dosaggio troponina
ECG
CT/RMN cerebrale in accordo con sospetto clinico di coinvolgimento neurologico
Prelievo per definire l'attività di ADAMTS13 e la ricerca anticorpi anti-ADAMTS13

PLASMIC SCORE

Lo score PLASMIC è stato sviluppato per predire la probabilità di un'attività di ADAMTS13 <10% nel paziente adulto con sospetta PTT.

Lo score assegna 1 punto a ciascuna delle seguenti variabili:

Conta piastrinica < 30.000/mmc
Presenza di emolisi (definita da una conta reticolocitaria > 2.5%, aptoglobina non dosabile o bilirubina indiretta >2 mg/dl)
Assenza di neoplasia attiva (neoplasia trattata nell'ultimo anno)
Paziente non sottoposto a trapianto d'organo o di cellule staminali emopoietiche
MCV < 90 fL
INR < 1.5
Creatinina < 2 mg/dl

Interpretazione: Secondo una recente revisione sistematica con metanalisi, uno score PLASMIC ≥ 5 è predittivo di un'attività ADAMTS13 < 10% con una sensibilità del 99% e un valore predittivo negativo tra il 97% e il 100% quando la prevalenza del deficit severo è pari o inferiore al 70% delle sospette PTT. Uno score PLASMIC basso (0-4) suggerisce che l'attività ADAMTS13 é > 10% con una specificità del 99%. Lo score PLASMIC non può essere usato come una prova definitiva della diagnosi di PTT ma è un valido strumento nelle situazioni dubbie in cui bisogna decidere riguardo alla terapia per PTT.[14,15]

Inviare prelievo per dosaggio ADAMTS13 se Plasmic Score ≥ 5

Linee Guida SIE 21.09. 2021

iTTP: historical treatment at the acute phase

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 until remission

=

Remission/survival could reach 85%, compared to almost no survival before

Unmet needs with historical treatment: suboptimal response

- **Exacerbations ~ 40% of patients**
- **Refractoriness ~ 10% of patients**

Coppo P, et al. Br J Haematol. 2006; Howard MA, et al. Transfusion. 2006

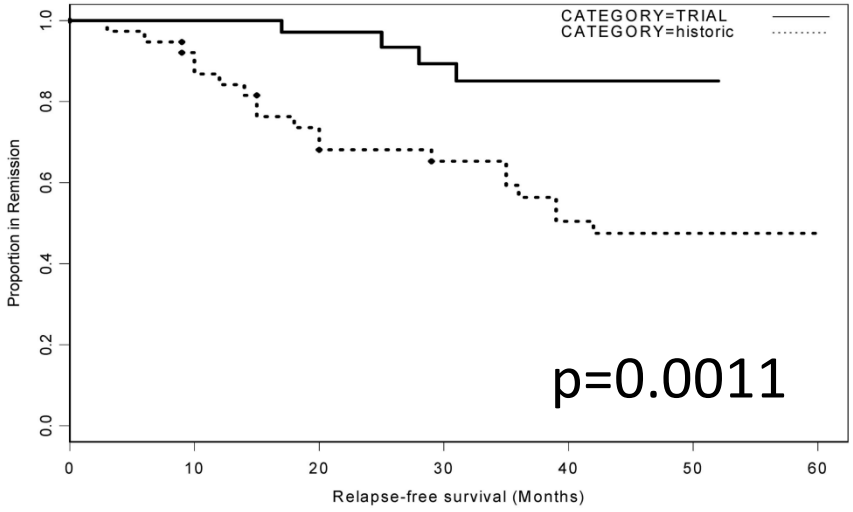
iTTP: Add of Rituximab to the historical treatment

A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura

Marie Scully,[1] Vickie McDonald,[2] Jamie Cavenagh,[3] Beverley J. Hunt,[4] Ian Longair,[1] Hannah Cohen,[1] and Samuel J. Machin[4]

[1]Department of Haematology, University College London Hospital, London, United Kingdom; [2]Haemostasis Research Unit, University College London, London, United Kingdom; [3]Department of Haematology, St Bartholomew's and the London Hospital, London, United Kingdom; and [4]Department of Haematology, Guys and St Thomas' National Health Service Foundation Trust, London, United Kingdom

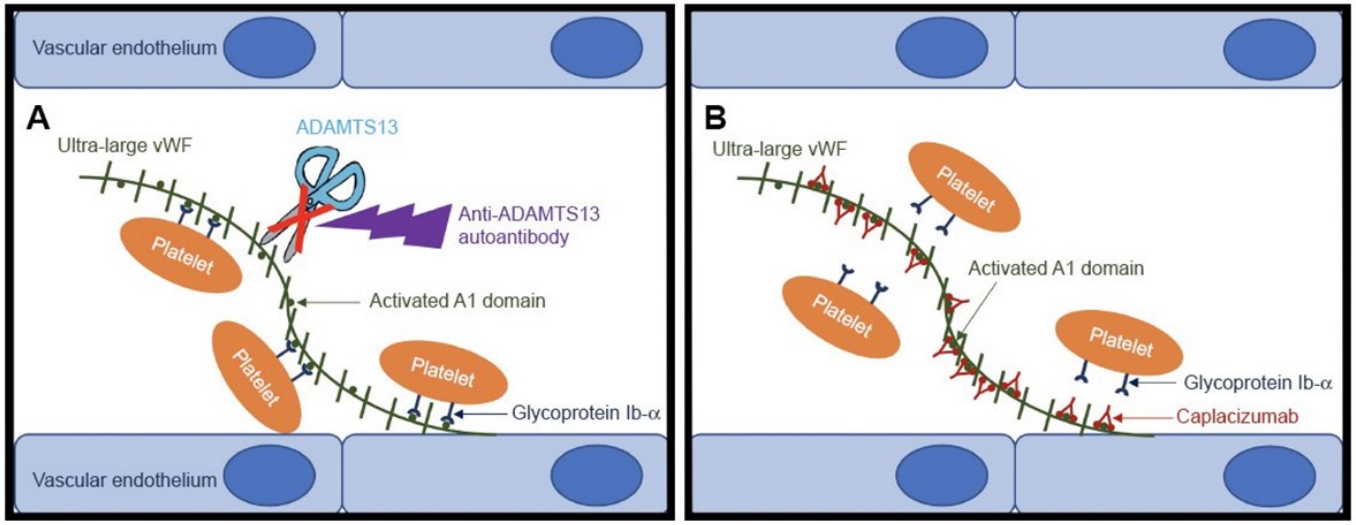
- The safety and efficacy of weekly rituximab 375 mg/m2 (x4), given within 3 days of acute TTP admission, with standard therapy (PEX and steroids) was evaluated.
- Inpatient stay was reduced by 7 days in the non-ICU trial cases compared to historical controls (P .04)
- **10% of trial cases relapsed**, median, 27 months (17-31 months), compared to **57% in historical controls**, median 18 months (3-60 months; P .0011)



Scully M et al, Blood 2011

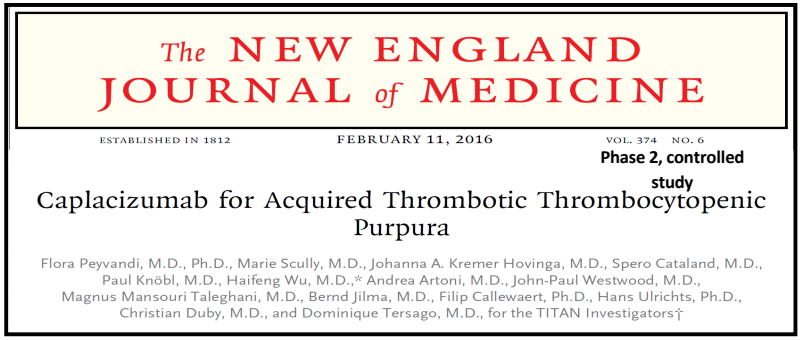
iTTP: Add of Caplacizumab to the historical treatment

- Caplacizumab (formerly ALX-0081 or ALX-0681) is a humanized single-variable domain immunoglobulin that recognizes the human von Willebrand factor (vWF) A1 domain and inhibits the vWF-platelet glycoprotein 1b-alpha (GP1b-α) interaction.



Elverdi T et al, Drug Design, Development and Therapy 2019

iTTP: Add of Caplacizumab to the historical treatment



The NEW ENGLAND JOURNAL of MEDICINE

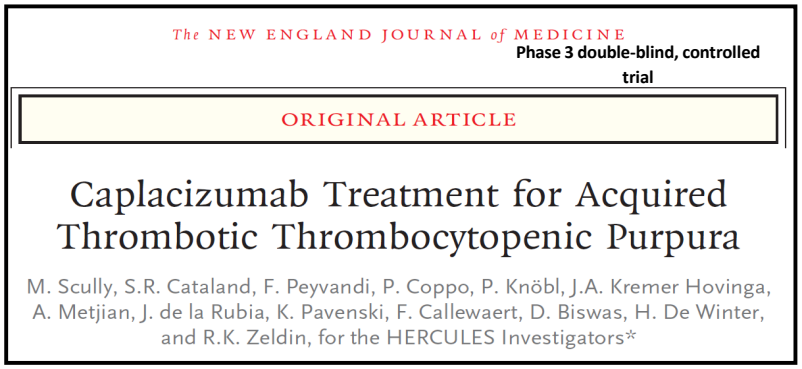
ESTABLISHED IN 1812 FEBRUARY 11, 2016 VOL. 374 NO. 6

Phase 2, controlled study

Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

Flora Peyvandi, M.D., Ph.D., Marie Scully, M.D., Johanna A. Kremer Hovinga, M.D., Spero Cataland, M.D., Paul Knöbl, M.D., Haifeng Wu, M.D.,* Andrea Artoni, M.D., John-Paul Westwood, M.D., Magnus Mansouri Taleghani, M.D., Bernd Jilma, M.D., Filip Callewaert, Ph.D., Hans Ulrichts, Ph.D., Christian Duby, M.D., and Dominique Tersago, M.D., for the TITAN Investigators†

- The **time to a response** was significantly reduced with caplacizumab as compared with placebo (39% reduction in median time, P=0.005).
- 3 patients in the caplacizumab group had an **exacerbation (11 patients in the placebo group).**
- **8 patients in the caplacizumab group** had a **relapse in the first month after stopping the study drug** (7 had ADAMTS13 activity that remained below 10%).
- **Bleeding-related adverse events** (mild to moderate in severity), were more common with caplacizumab than with placebo (54% of patients vs. 38%)



The NEW ENGLAND JOURNAL of MEDICINE

Phase 3 double-blind, controlled trial

ORIGINAL ARTICLE

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura

M. Scully, S.R. Cataland, F. Peyvandi, P. Coppo, P. Knöbl, J.A. Kremer Hovinga, A. Metjian, J. de la Rubia, K. Pavenski, F. Callewaert, D. Biswas, H. De Winter, and R.K. Zeldin, for the HERCULES Investigators*

- The **median time to normalization of the platelet count** was shorter with caplacizumab than with placebo (2.69 days vs. 2.88 days, P=0.01)
- The percentage of patients with a **composite outcome event (death, recurrence, major thromboembolic events)** was 74% lower with caplacizumab than with placebo (12% vs. 49%, P<0.001).
- The percentage of patients who had a **recurrence of TTP** at any time during the trial was 67% lower with caplacizumab than with placebo (12% vs. 38%, P<0.001).
- **Refractory disease** developed in 3 patients in the placebo group.
- Patients who received caplacizumab needed **less plasma exchange and had a shorter hospitalization** than those who received placebo.
- The most common adverse event was **mucocutaneous bleeding** (65% of the patients in the caplacizumab group and in 48% in the placebo group)

iTTP: Add of Caplacizumab to the historical treatment

	TITAN[1]	HERCULES[2]	GERMAN[3]	FRANCE[4]	SPAIN[5]	USA[6]	UK[7]
N=	39	73	119	180	76	1096	39
Time to persistent PLT>150 (d; median, IQR)	4.9 (3.2/6.6)	2.9 (1.8/2.8)	12 (6/20)	12 (6/17)	14 (7/21)	Not reported	6 (4/10)
Refactoriness (no PLT normalization within 5 days)	Not reported	4%	11%	18%	14.1%	Not reported	0%
Exacerbations	28%	38%	43%	44%	20.5%	Not reported	0%
Deaths	5%	4%	4%	6.7%	7.7%	8%	0%
TPE days (medians, IQR)	11.7 (2–43[a])	7 (3–46)	8 (5/14)	10 (6/16)	14 (7/21.5)	Not reported	9 (8/16)
Hospital stay (d; medians, IQR)	Not reported	12 (4–53)	18 (11/25)	22 (15/30)	19 (12/27)	11 (7/20)	14 (9/17)
Rate of bleeding **Rate of severe bleeding**	38% 5.4%	48% 1.4%	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	0% 0%

- Caplacizumab was efficacious in iTTP and curtailed the time of active iTTP only when used in **the first-line therapy within 72 hours and until at least partial ADAMTS13-activity remission.**
- Caplacizumab use resulted in **significant absolute risk reduction of 2.87% for iTTP-related mortality** (number needed to treat 35) and a **relative risk reduction of 59%.**
- Caplacizumab should be used in first line and until ADAMTS13-remission, **lowers iTTP-related mortality and refractoriness, and decreases the number of daily TPE and hospital stay.**

Völker et al. J. Thromb Haemost. 2023

iTTP: Standard of care

PEX
Plasma Exchange

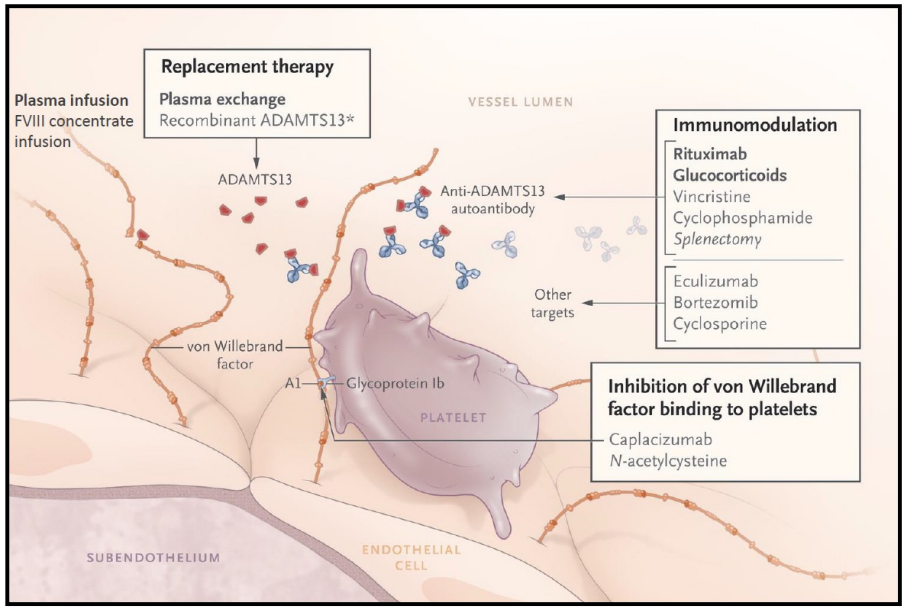
- The exchange plasma volume should be equal to 1-1.5 the patient's plasma volume (40-60 ml/kg)
- Discontinue until platelet count normalizes.

Glucocorticoids

- Prednisone 1 mg/kg (max 100 mg/day). (in severe cases Methylprednisolone 10 mg/kg/day day 1-3)
- Maintain full dosage up to ADAMTS 20-30%, then taper off in 3 weeks

Caplacizumab

- I IV dose within 30 min of I PEX
- II dose and subsequent sc within 2 hours of PEX
- Continue with 1 fl/day for at least 30 days after the last PEX
- Suspend when ADAMTS13 >20% in 2 determinations (recommended weekly monitoring)



Adapted from Veiradier, NEJM 2016

* In Italy, **Rituximab** can be used only as second line or pre-emptive therapy

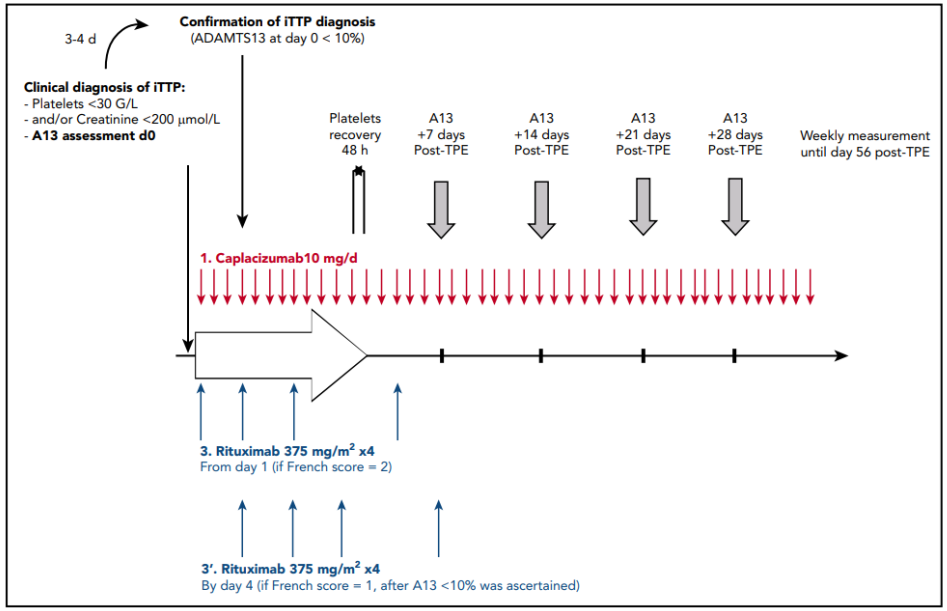
Linee Guida SIE, 21.09.2021

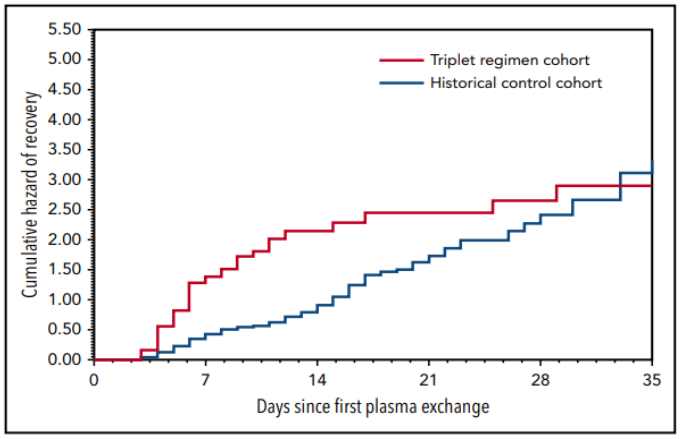
iTTP: Rituximab first line (triplet regimen)

A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavorable outcomes in immune-mediated TTP

Paul Coppo,[1-3] Michael Bubenheim,[4] Elie Azoulay,[1,5,6] Lionel Galicier,[1,6,7] Sandrine Malot,[1] Naïke Bigé,[1,8] Pascale Poullin,[1,9] François Provôt,[1,10] Nihal Martis,[11] Claire Presne,[1,12] Olivier Moranne,[13] Ruben Benainous,[14] Antoine Dossier,[15] Amélie Seguin,[1,16] Miguel Hié,[1,17] Alain Wynckel,[1,18] Yahsou Delmas,[1,19] Jean-François Augusto,[1,20] Pierre Perez,[1,21] Virginie Rieu,[1,22] Christelle Barbet,[1,23] François Lhote,[24] Marc Ulrich,[25] Anne Charvet Rumpler,[1,26] Sten de Witte,[27] Thierry Krummel,[1,28] Agnès Veyradier,[1,29,30] and Ygal Benhamou,[1,31,32] for the French Reference Center for Thrombotic Microangiopathies

BLOOD, 2021





Outcome	Triplet regimen (N = 90)	Historical cohort (N = 180)	P
Primary outcome			
Composite of death and refractoriness			
All patients	2 (2.2%)	22 (12.2%)*	.01
According to French Severity score			
0-2	2 (2.8%)	15 (8.3%)	<.01
3-4	0	7 (33%)	
Secondary outcomes			
Death	1 (1.1%)	12 (6.7%)	.06
Refractoriness	1 (1.1%)	16 (18%)†	.01
Exacerbations	3 (3.4%)	70 (44%)	<.01
Time to durable platelet count recovery	5 (4-6)	12 (6-17)	<.01
Number of daily TPE until remission	5 (4-7)	10 (6-16)	<.01
Volume of plasma (L) until remission	24.2 (18.3-30.2)	44.4 (26.3-74.3)	<.01
Time to ADAMTS13 activity > 20% (days)	28 (14-42)	48 (24-83)	<.01
Length of hospitalization (days)	13 (9-19)	22 (15-30)	.01
Thromboembolic events	11 (12%)	20 (11.1%)	.79

- A triplet regimen reduces unfavorable outcomes in immunemediated TTP and alleviates the burden of care
- Caplacizumab and Rituximab should be considered complementary
- Patients treated with the triplet regimen have a favorable outcome irrespective of disease severity on diagnosis

iTTP: Caplacizumab future directions
Alternate day dosing

Alternate-day dosing of caplacizumab for immune-mediated thrombotic thrombocytopenic purpura J Thromb hemost 2022

Lucas Kühne[1,2] | Jessica Kaufeld[3] | Linus A. Völker[1,2] | Ralph Wendt[4] | Ulf Schönermarck[5] | Holger Hägele[1,2] | Thomas Osterholt[1,2] | Dennis A. Eichenauer[6] Markus Bieringer[7] | Anke von Bergwelt-Baildon[5] | Michael Fischereder[5] | Veronika Buxhofer-Ausch[8,9] | Jan Menne[3] | Paul T. Brinkkoetter[1,2] | Paul Knöbl[10]

- Retrospective cohort of 25 iTTP patients, treated according to labeling with daily caplacizumab and additionally received **rituximab** and steroids.
- Median time of daily, post-PEX caplacizumab treatment until introduction of alternate –day dosing was **11 days (1-230)**
- **20 patients on an alternate-day caplacizumab regimen showed persisting stable platelet counts without any signs of iTTP exacerbations or relapse.**
- Exacerbations or relapse occurred solely in patients with a **delayed recovery of ADAMTS13 activity** (≥ 24 days post PEX) and in whom **alternate day-dosing was introduced or terminated early** (≤ 19 days of daily caplacizumab post PEX until treatment modification).
- Extension of caplacizumab application intervals from daily to alternate-day dosing may be safely considered in **selected patients after 3 or 4 weeks of daily treatment.**

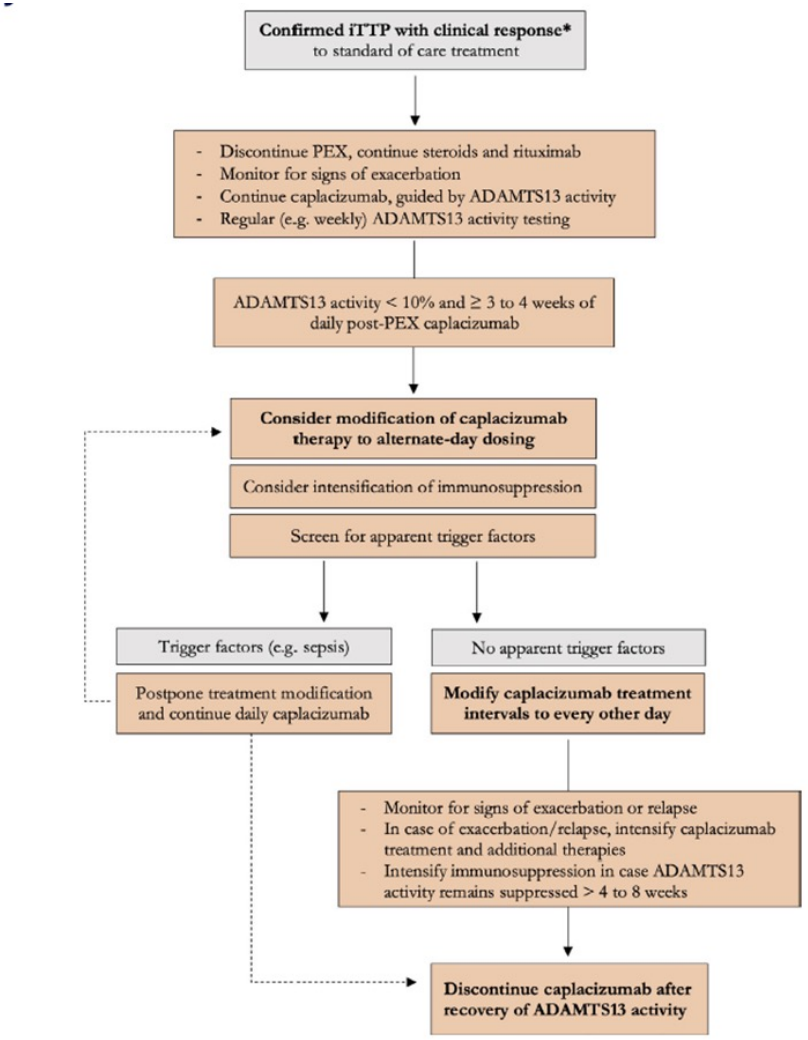
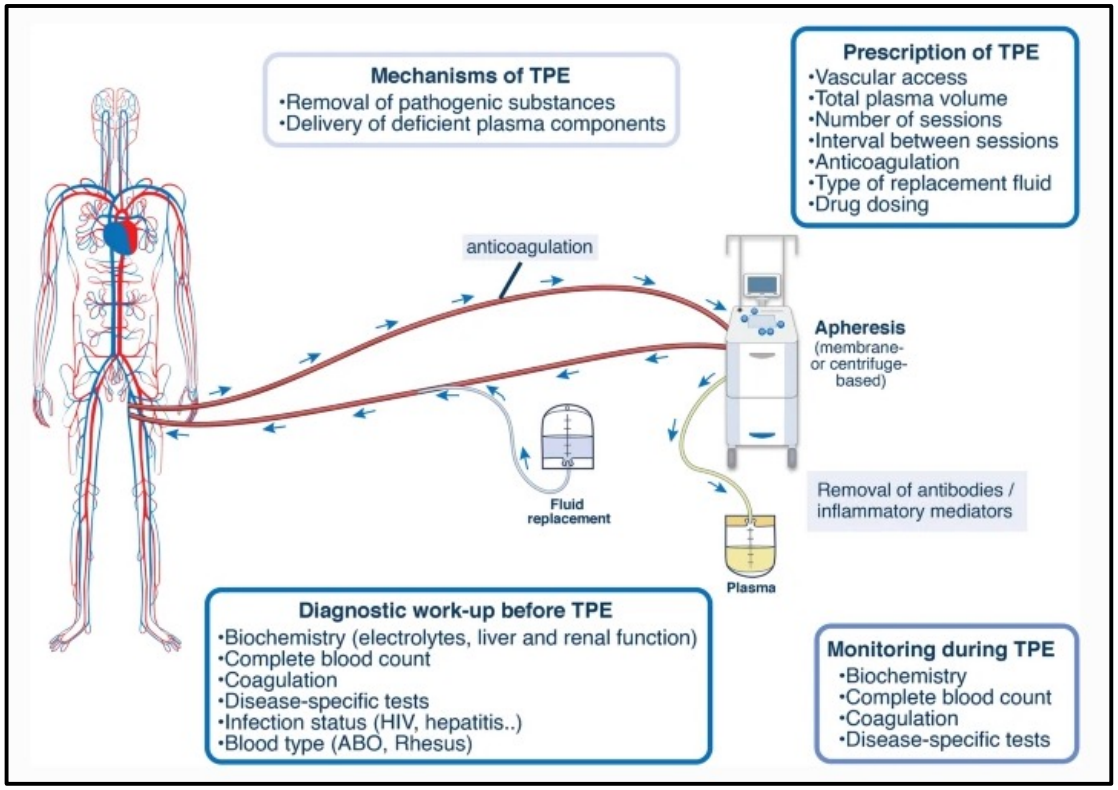


FIGURE 5 Proposed treatment algorithm for modification of daily caplacizumab therapy to alternate-day dosing. *Clinical response defined as sustained platelet count ≥150 × 10^9/L and LDH <1.5 times ULN.[17] LDH, lactate dehydrogenase; ULN, upper limit of normal

iTTP: Therapeutic Plasma Exchange (TPE)

Effects of TPE:

- Removal of UL-VWF, anti-ADAMTS13 autoantibodies, cell fragments, sludge, cytokines, NETs, etc.
- Replacement of ADAMTS13 and regular composed VWF



Rock GA et al, N Engl J Med. 1991; Bauer PR et al, Intensive Care Medicine 2022

iTTP: Therapeutic Plasma Exchange (TPE)

Requirements for TPE:

- Large-lumen central venous line
- Large amounts of frozen plasma of matched blood group
- Experienced staff
- Adequate equipment (centrifuge-based plasma separation preferred)
- Time slots
- Monitoring, often ICU necessary

Complications:

- Inadvertent arterial punction
- Bleeding, hematoma, airway compression
- Arrhythmia, VT, (VF)
- Vasovagal symptoms, syncope, etc.
- Allergic reactions to local anesthesia
- Pneumothorax, hematothorax
- Nerve lesions
- Catheter infections, sepsis
- Thrombosis
- Patient discomfort: pain, Trendelenburg position
- Agitated neurologic patients need sedation

Buckenmayer A, et al. J Vasc Access. 2023; Ullman AJ, et al. Pediatrics. 2015

iTTP: Limitations and disadvantages of TPE

Symptomatic procedure (Does not target underlying pathophysiology)

Adverse effects

- ✓ Allergic reactions, urticaria, flush
- ✓ Citrate toxicity, hypocalcemia
- ✓ Hemodynamic instability
- ✓ Dyspnea, respiratory problems, transfusion-induced lung injury
- ✓ Fever, nausea, headache, cramps, seizures
- ✓ Immunogenicity, hemolysis
- ✓ Hemorrhage, clotting
- ✓ TTP exacerbations
- ✓ Enhanced shear when hollow-fiber plasma separators used (may lead to TTP exacerbations)

Time-consuming preparations

- ✓ Blood group typing
- ✓ Ordering frozen plasma, large amounts of plasma needed (daily 16–20 units)
- ✓ Allocating time/staff/devices/resources
- ✓ Venous access – central venous line

Limited efficacy

- ✓ High rates of delayed response, exacerbations, and refractoriness
- ✓ Still a considerable rate of mortality

Basic-Jukic N, et al. Ther Apher Dial. 2005; Rizvi MA, et al. Transfusion. 2000; Shemin D, et al. J Clin Apher. 2007

iTTP: Management without TPE?

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CORRESPONDENCE

2019 Jul 4

Caplacizumab Therapy without Plasma Exchange for Acquired Thrombotic Thrombocytopenic Purpura

Deepak P. Chander, Michelle M. Loch, Spero R. Cataland, James N. George

Case report from patient declining blood products show successful outcomes without PEX

- Caplacizumab, together with glucocorticoids and rituximab, may be effective treatment for patients with TTP who are unable or unwilling to undergo plasma
- In these patients, a prompt response to the receipt of caplacizumab may suggest that subsequent initiation of TPE is unnecessary, which would avert the potential risks associated with plasma exchange.

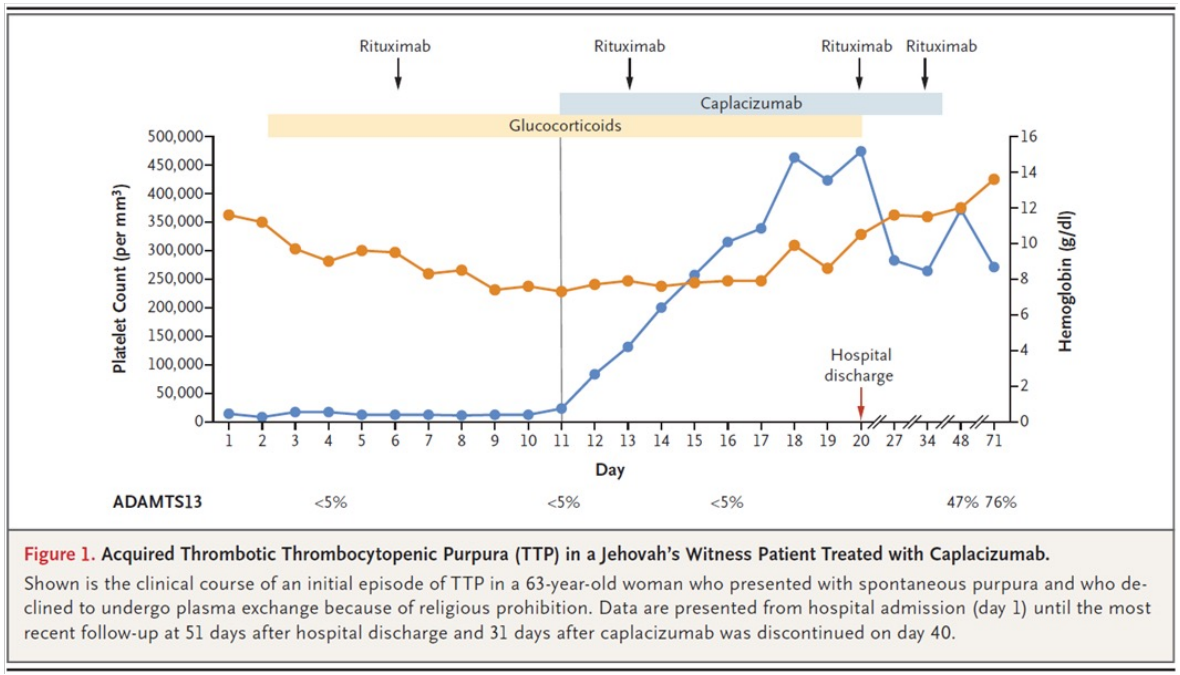


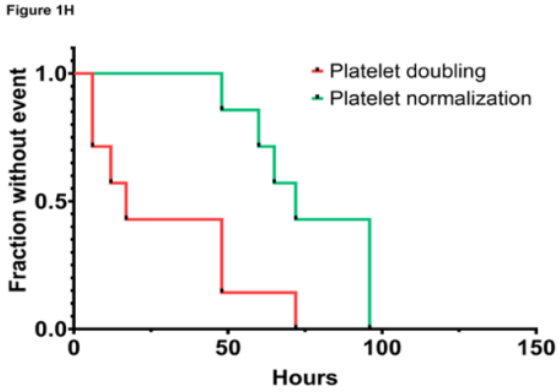
Figure 1. Acquired Thrombotic Thrombocytopenic Purpura (TTP) in a Jehovah's Witness Patient Treated with Caplacizumab.
Shown is the clinical course of an initial episode of TTP in a 63-year-old woman who presented with spontaneous purpura and who declined to undergo plasma exchange because of religious prohibition. Data are presented from hospital admission (day 1) until the most recent follow-up at 51 days after hospital discharge and 31 days after caplacizumab was discontinued on day 40.

iTTP: Management without TPE?

Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab

J Thromb Haemost. 2020;18:3061–3066.

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]



Six patients selected from among >60 caplacizumab treated iTTP patients from Germany and Austria

Seven episodes of iTTP, treated with caplacizumab and immunosuppression (rituximab), but **entirely without plasma exchange**

- Rapid and robust increase of platelet counts already after the first dose of caplacizumab
- Thus, clinical decision that TPE was no more needed
- Doubling of platelet counts within 17 hours (median)
- Platelet counts normalized (>150 G/L) after median 84 hours (=3.5 days)
- LDH improved in parallel to the platelet counts, indicating resolving microangiopathy
- All patients recovered without sequelae or treatment-related adverse reactions

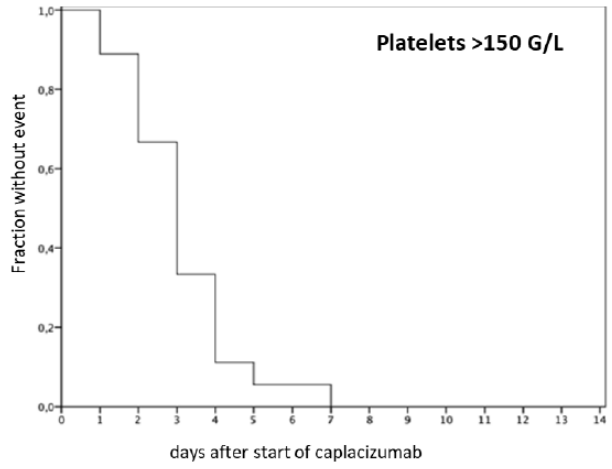
iTTP: Management without TPE?

Austrian Data on TPE-free iTTP Treatment

(median, range)

	N=23
Male/female	9 / 14
Age, years	43 (24 – 84)
Initial PLT, G/L	9 (4–75)
Initial hemoglobin, g/dL	8.5 (5.7–15.4)
Initial LDH, U/L	878 (223–2,500)
Initial creatinine, mg/dL	1.1 (0.6–1.8)
Initial troponin, ng/L	91 (0–358)
Baseline ADAMTS13 activity (%)	0 (0–7.6)
Baseline ADAMTS13 inhibitor (BU/mL)	2.9 (1.1–55)
Triggers:	
• **Unknown**	11
• **Active virus infections (EBV; CMV; hepatitis B, SARS-Cov2)**	8
• **Bacterial infections**	3
• **Neoplasms**	1

Admission to first dose of caplacizumab, days	0 (-1–5)
Admission to first rituximab, days	3.5 (1–18)
Doubling of PLT, days	1 (0–4)
PLT > 150 G/L	3.5 (1–7)



Knöbl P, et al. Management of thrombotic thrombocytopenic purpura (TTP) without plasma exchange: an update on the Austrian experience. Presented at ISTH 2022

iTTP: Management without TPE?

Therapeutic plasma exchange-free treatment for first-episode TTP: A systematic review

Transfusion and Apheresis Science 2023

Jiang Wang [1], Fu Cheng [1], Yingying Niu, Lingli Yan, Jiaheng Li, Bin Tan [*], Li Qin [*]

- 14 case reports, 3 case series, 5 retrospective study
- The information of 23 patients was included

Treatment regimen and outcomes in patients with TTP.

Therapeutic regimen	outcome			Total
	relapse	death	remission	
TPE with CSP+glucocorticoid	3		2	5
caplacizumab+rituximab+glucocorticoid			4	4
CSP infusion+glucocorticoid			3	3
no treatment		1	1	2
IVIG+glucocorticoid			1	1
TPE with albumin+TPE with CSP+IVIG+glucocorticoid			1	1
glucocorticoid+immunosuppressant			1	1
rTM			1	1
FFP infusion+IVIG+glucocorticoid			1	1
TPE with albumin + rituximab + IVIG + glucocorticoid			1	1
TPE with albumin + rituximab + IVIG + glucocorticoid + immunosuppressant			1	1
TPE with albumin + rituximab + glucocorticoid + immunosuppressant + pegylated bovine			1	1
TPE with albumin + rituximab + glucocorticoid + immunosuppressant			1	1
Total	3	1	19	23

- In terms of the **outcomes** of TTP patients without TPE in this study, 3 cases relapsed, 1 case died of cardiac arrest before treatment. The rest of the other patients recovered
- **Mortality rates** reported in 4 retrospective studies: pooled results found **no significant difference** in mortality between patients who received TPE and those who did not (odds ratio [OR]: 0.54, 95 % CI: 0.23–1.28, P = 0.16, I2 = 61 %)

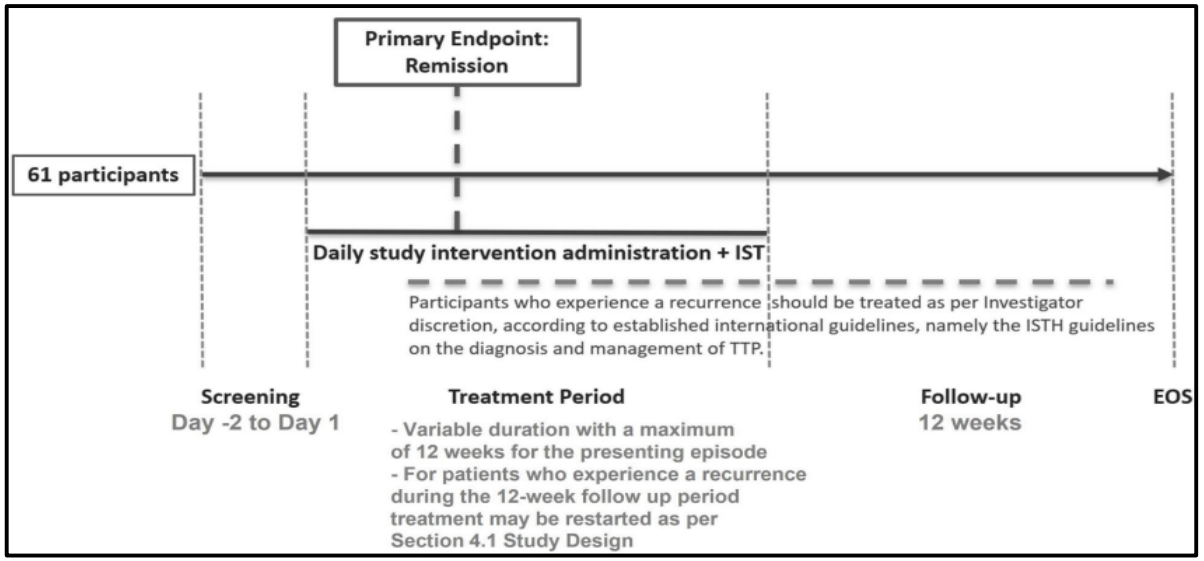
iTTP: Management without TPE?

MAYARI

An open-label, single-arm, multicenter study to evaluate the efficacy and safety of Caplacizumab and immunosuppressive therapy without first-line therapeutic plasma exchange in adults with immune-mediated thrombotic thrombocytopenic purpura (NCT05468320)

- **Primary objective:** To evaluate the efficacy of caplacizumab in combination with immunosuppressive therapy (IST) without therapeutic plasma exchange (TPE) in adults with immune mediated thrombotic thrombocytopenic purpura (iTTP)

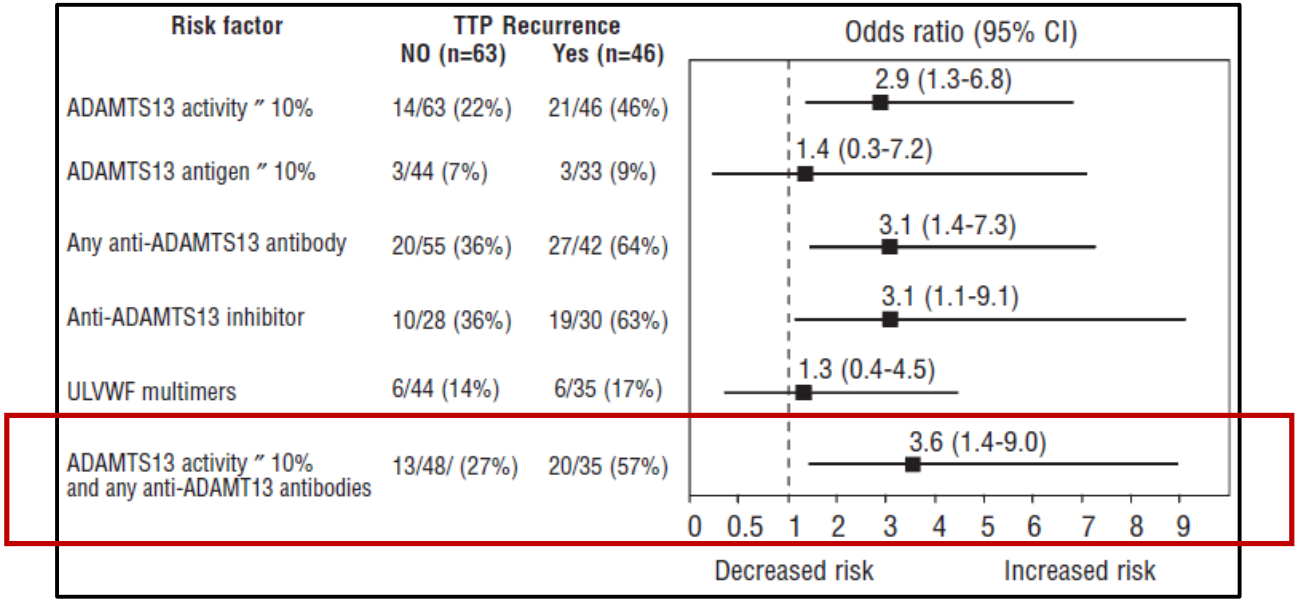
- **Primary endpoint:** Proportion of participants achieving Remission without requiring TPE during the overall study period



iTTP: Long-term relapses

- Up to 40% of survivors had a persistent severe (<10%) ADAMTS13 deficiency after remission achievement **BEFORE the era of rituximab frontline**. Among them, **38.5% experienced a relapse within a 1-year period**

- The presence during remission of **both severe ADAMTS13 deficiency and anti-ADAMTS13 antibodies increased the likelihood of recurrence 3.6 times** (95% confidence interval 1.4 to 9.0; p=0.006).

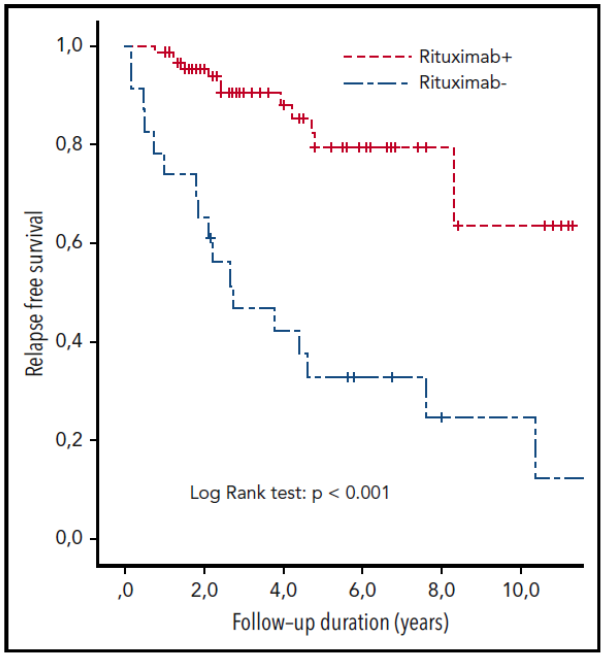


Ferrari S et al, Blood 2007, Peyvandi F et al, Haematologica 2008

iTTP: Prevention of long-term relapses

Pre-emptive Rituximab

- Without preemptive treatment: 17/23 clinical relapses (74%) (multiple in 11 patients) after a median follow-up of 7 years
- Cumulative incidence of relapse: 0.33/year without Rituximab, 0/year with Rituximab (p <.001)
- Rituximab has an acceptable long-term safety profile (12 years follow up)
- Experience from the UK and France has shown high response rates with **~80% cases normalising ADAMTS13 levels** if given pre-emptively, although **~20% of patients failed to respond to rituximab alone**



Intensive Rituximab regimen

- Median duration: 2 years (range 1 - 6)
- Median infusions of Rituximab: 8 (range 5 – 13)
- Rituximab was administered every 2-3 months (8 patients) or twice a year (5 patients)
- Response > 75%

Alternative immunosoppressive treatment:

- Cyclosporine, azathioprine, MMF, vincristine cyclophosphamide
- Other anti-CD20 MoAb (obinutuzumab, ofatumumab)
- Daratumumab

Jestin M, et al. Blood 2018; Barba et al, BJH 2020; Doyle AJ, et al. Br J Haematol. 2022; Van der Berg J, et al. Blood Adv. 2022

Conclusions

- The **triple therapy** consisting of daily plasma exchange, caplacizumab, and immunosuppressives (e.g., steroids and rituximab) should be considered the **standard of care** today for all patients with confirmed iTTP or those with high probability of iTTP as long as plasma ADAMTS13 evaluation is obtainable for confirmation.
- **Plasma exchange** is still the standard of care for all patients with iTTP, and has reduced the rate of mortality from >90% to 10–20%, but it is a **complex procedure**, with **potential adverse effects**
- **Caplacizumab has clearly improved the outcome of iTTP**
- **Exacerbations and relapses** in iTTP can be efficiently prevented with Caplacizumab and Rituximab
- **Pre-emptive Rituximab** significantly reduces iTTP relapse; the safety profile seems acceptable, even in patients receiving Rituximab for a long time
- **Novel therapies** are needed **to improve the rate of exacerbations** in iTTP
- **iTTP management without TPE is possible**