Nous tractaments de la púrpura trombocitopènica trombòtica adquirida

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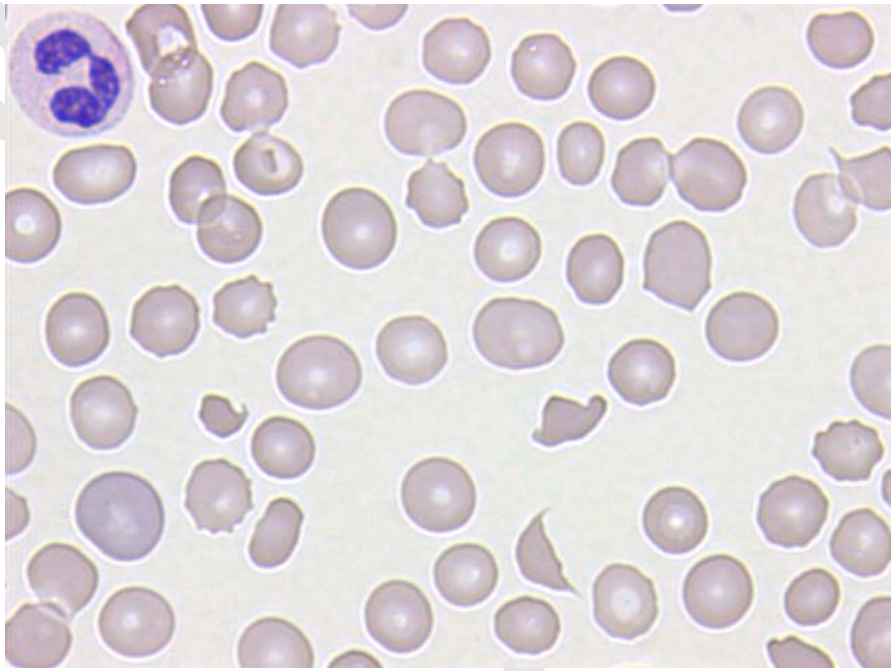
aTTP



HL , Female, 23 years-old

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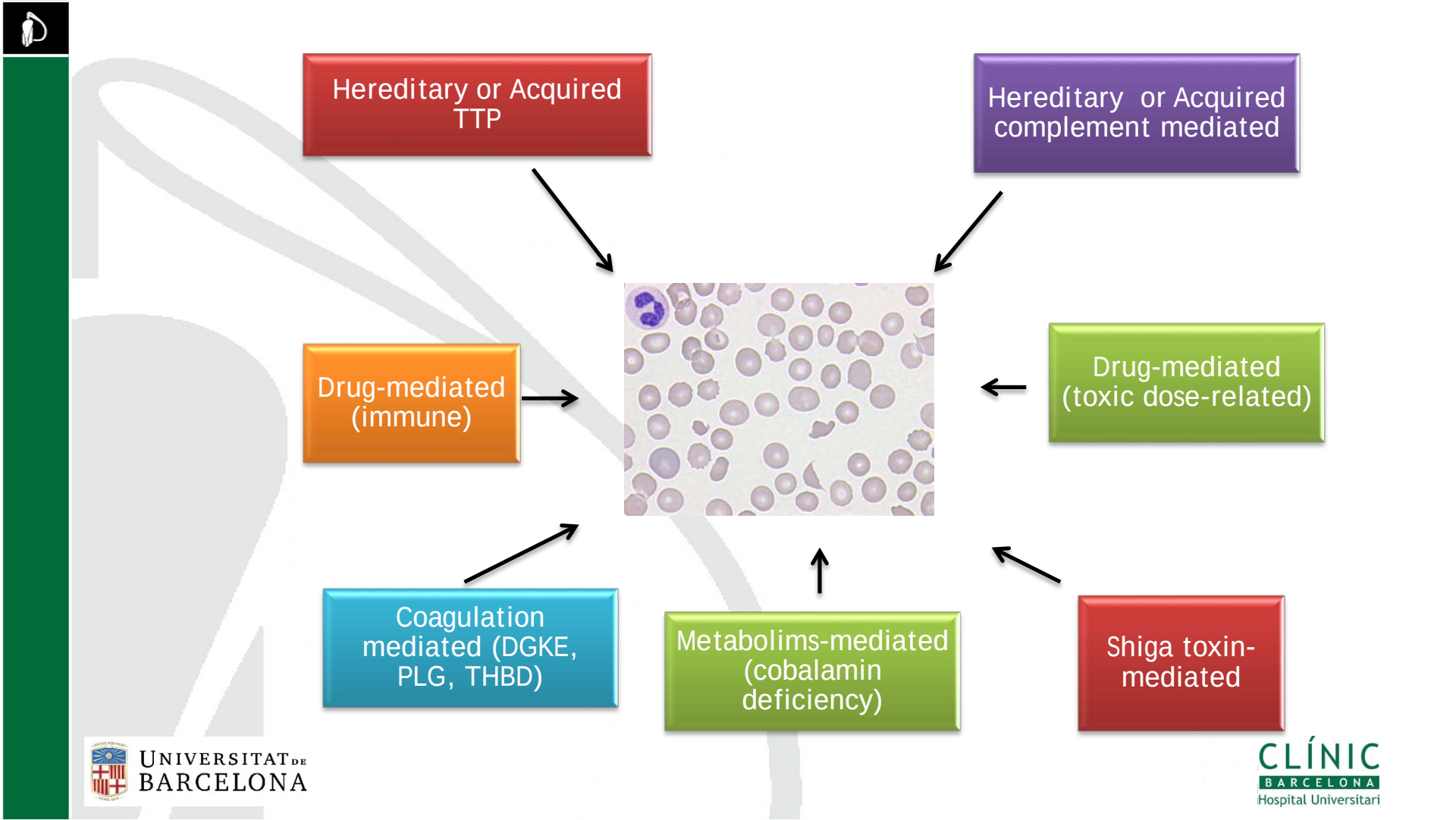
Thrombotic Microangiopathies

- Disorders defined by the presence of a microangiopathic hemolytic anemia (with the characteristic hallmark of schistocytes in the peripheral blood smear), thrombocytopenia and organ malfunction of variable intensity


Hereditary or Acquired TTP
Hereditary or Acquired complement mediated
Drug-mediated (immune)
Drug-mediated (toxic dose-related)
Coagulation mediated (DGKE, PLG, THBD)
Metabolims-mediated (cobalamin deficiency)
Shiga toxin-mediated

TMA: etiology

- Primary:
  - Thrombotic thrombocytopenic purpura (TTP):
    - Acquired:
    - Congenital:
  - Atypical hemolytic uremic syndrome (aHUS):
- Secondary:
  - Connective tissue diseases and their allied diseases:
  - Malignancies:
  - Hematopoietic stem cell transplantation:
  - Drugs:
  - E Coli O157:H7 infection:
  - Pregnancy:
  - Other:

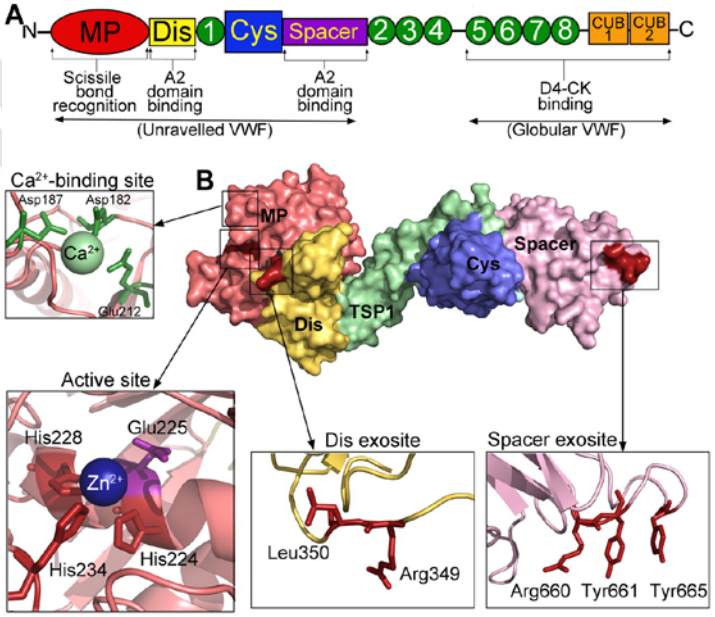
Fujimura Y, *et al*. Intern Med 2010; 49:7-15

TMA: etiology and frequencies (Japanese registry)

- Primary: 49.5%
  - Thrombotic thrombocytopenic purpura (TTP):
    - Acquired: 30.9%
    - Congenital: 4.5%
  - Atypical hemolytic uremic syndrome (aHUS): 11.5%
- Secondary: 50.5%
  - Connective tissue diseases and their allied diseases: 24.0%
  - Malignancies: 6.6 %
  - Hematopoietic stem cell transplantation: 5.9%
  - Drugs: 3.8%
  - E Coli O157:H7 infection: 3.4%
  - Pregnancy: 1.6%
  - Other: 5.0%

Fujimura Y, *et al*. Intern Med 2010; 49:7-15

ADAMTS13 (*a disintegrin-like and metalloprotease with thrombospondin repeats*”



Crawley JTB, *et al*. Blood 2011; 118: 3212-3221

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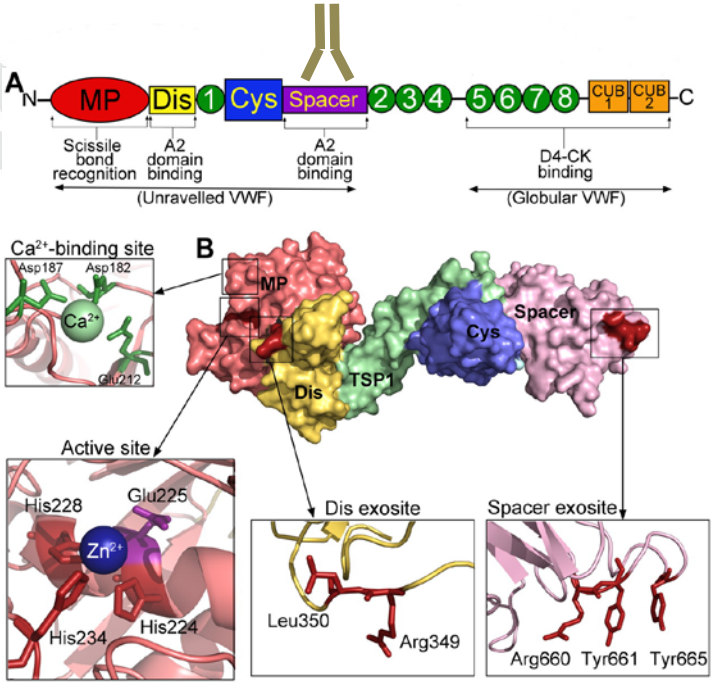
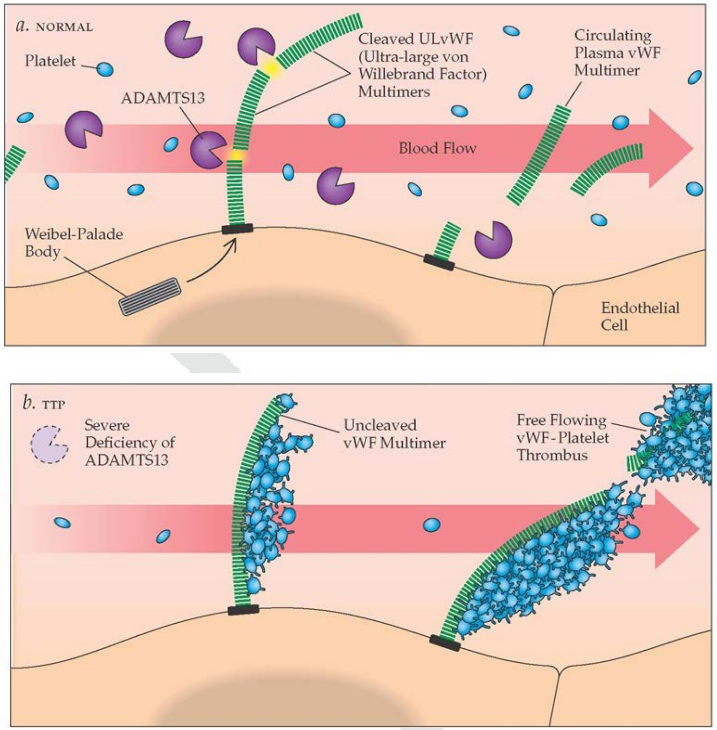
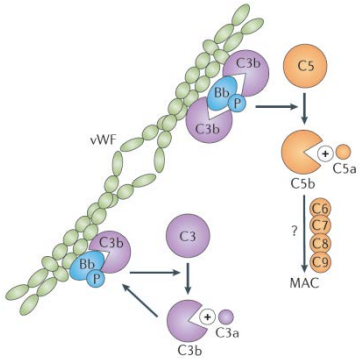


Crawley JTB, *et al*. Blood 2011; 118: 3212-3221

TTP: Pathogenesis





http://what-when-how.com/acp-medicine/platelet-and-vascular-disorders-part-2/
Kremer Hovinga JA, *et al*. Nat Rev Dis Primers. 2017:17020. doi: 10.1038/nrdp

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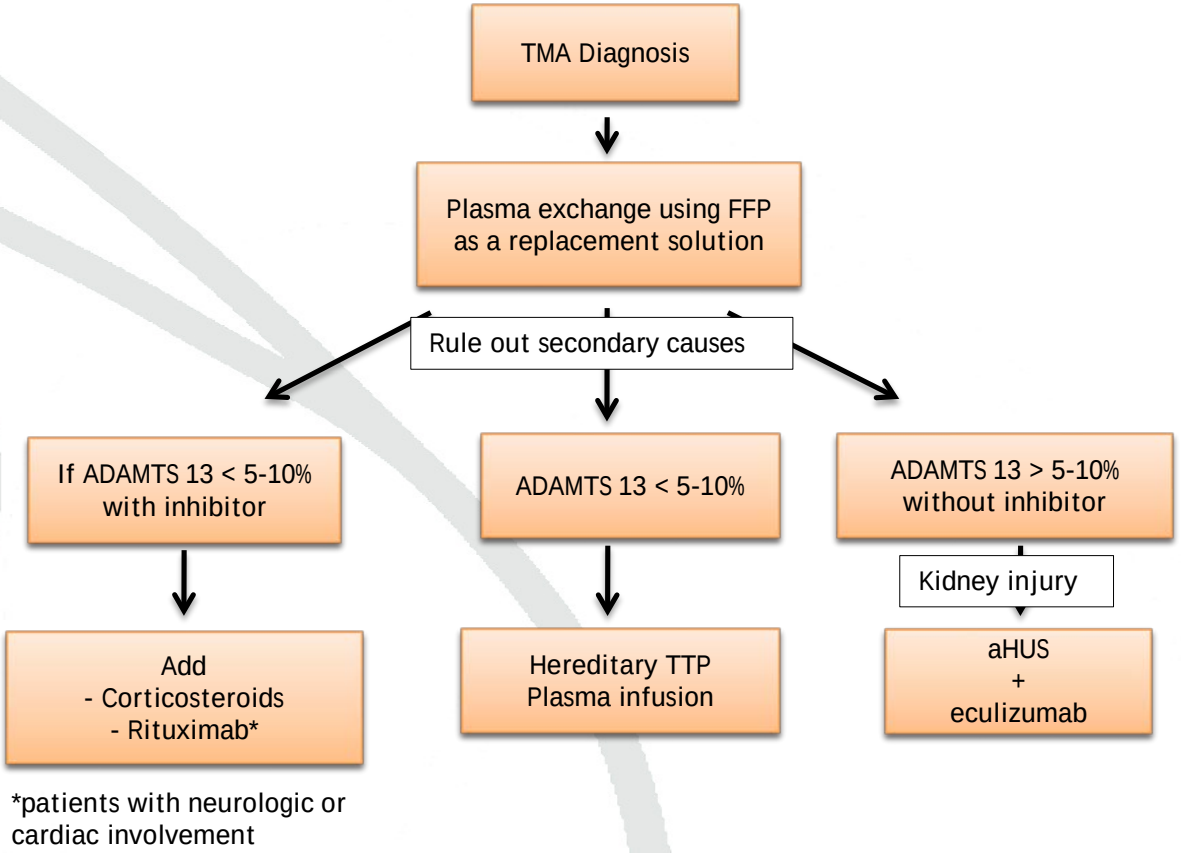
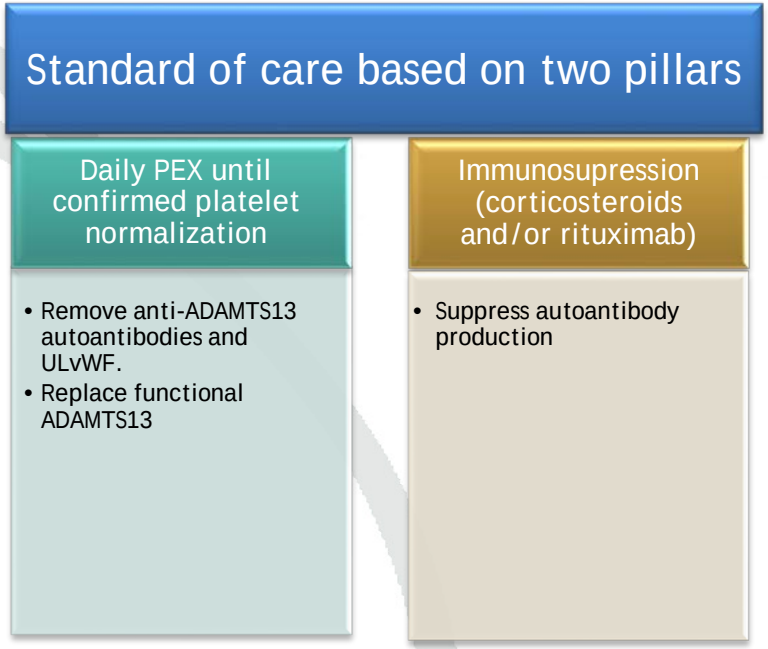


Scully M, *et al*. Br J Haemat 2014; 64: 759-766

Mainstay for the treatment of aTTP



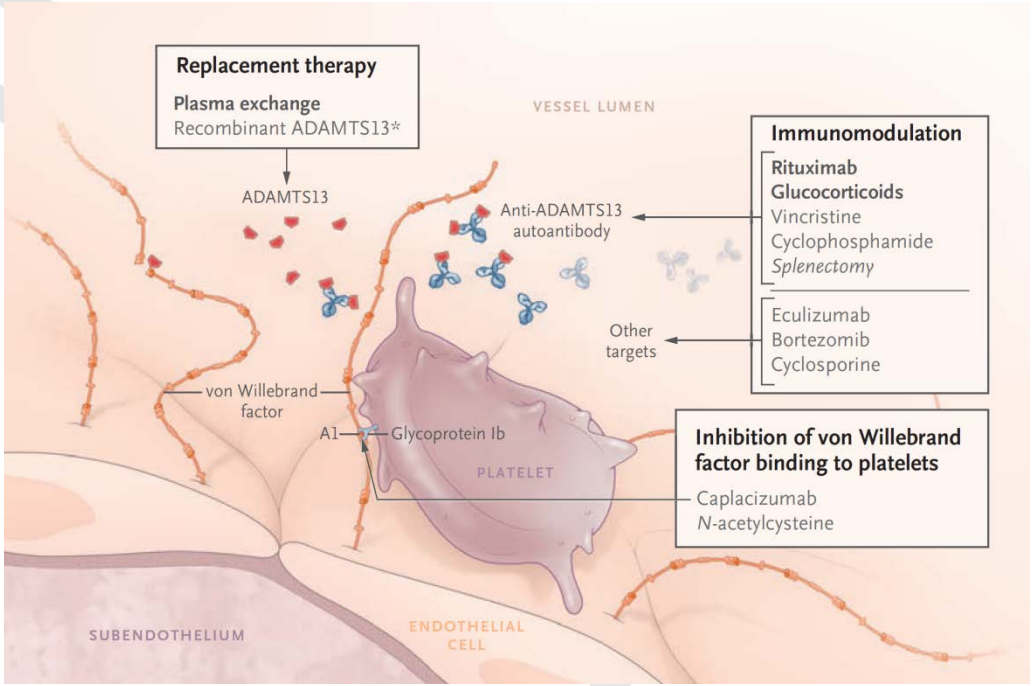
Treatment Outcome

Table 2 | **Reports involving ≥10 patients with acquired, immune-mediated TTP treated with rituximab in the acute phase**

Refs	n	Complete remission achieved (%)	Median days to complete remission (range)	History of previous iTTP (%)	Relapse (%)	Median months to relapse (range)	Serious adverse events
Scully *et al.*[154]*	25	100	11 (7–21)	44	0	NA	One fatal pneumonia, after achieving complete remission, and one morbilliform rash
Jasti *et al.*[155‡]	12	83	18 (14–41)	8	8	23	One varicella zoster virus transverse myelitis and encephalitis
Ling *et al.*[156‡]	13	92	NA	54	0	NA	None
de la Rubia *et al.*[157‡]	24	87.5	14 (7–35)	42	12.5	29 (7–29)	None
Scully *et al.*[158§]	40	82.5	12 (NA)	15	10	27 (17–31)	None
Froissart *et al.*[159]*	22	82	12 ± 6.7	14	14	24 (20–36)	None
Page *et al.* [160‡,‖]	16	100	NA	0	12.5	30 and 118.8‖	Formally none; however, two patients died of systemic lupus erythematosus during the study
Vazquez-Mellado *et al.*[161*,§,¶]	11	100	NA	9	9	8	None

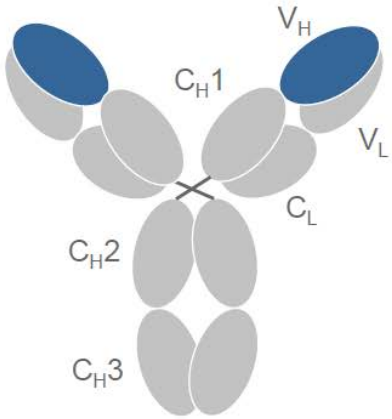
iTTP, acquired immune-mediated thrombotic thrombocytopenic purpura; NA, data not available. *Prospective. ‡Retrospective. §Rituximab as front-line therapy. ‖Only survivors are reported (two additional patients died). ¶Rituximab dosage was lower than in all other studies.

Current and Emerging Therapeutic Approaches for aTTP

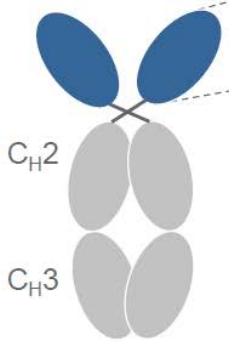


Veyradier A. N Engl J Med 2016;59-766

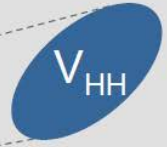
Nanobodies



Conventional antibodies



Heavy chain only antibodies

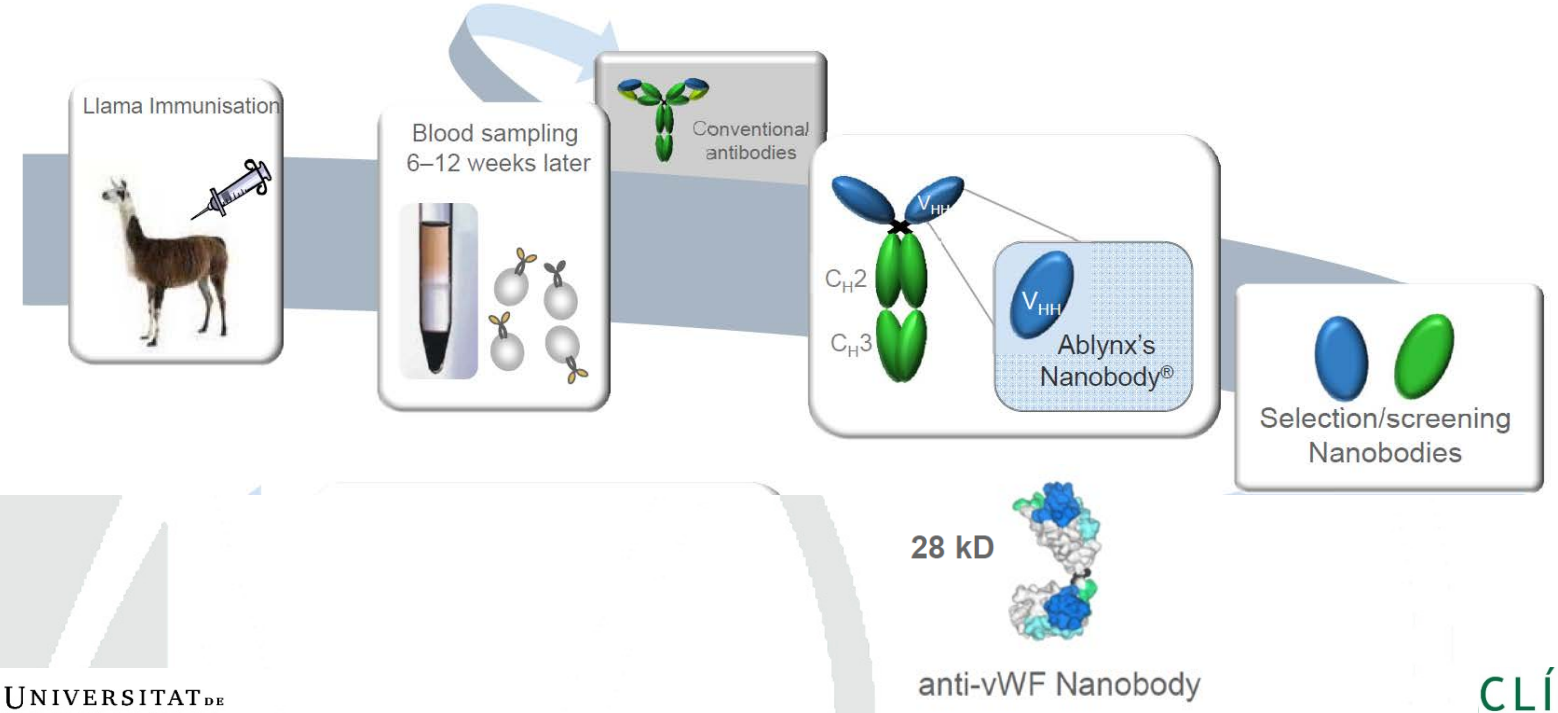


12-15kDa

Ablynx's Nanobody

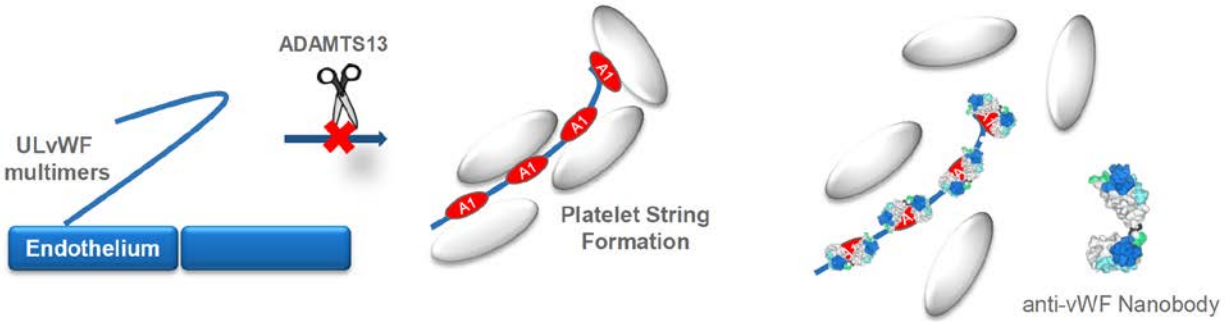
- small
- robust
- sequence homology comparable to humanised/human mAbs
- easily linked together
- nano- to picomolar affinities
- intractable targets
- multiple administration routes
- manufacturing in microbial cells

Nanobody Development

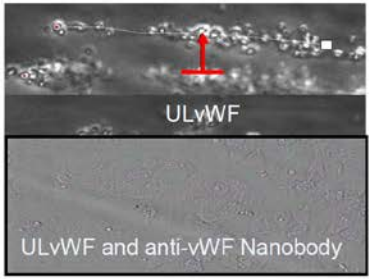


Anti-VWF Nanobody

anti-vWF Nanobody blocks the platelet – ULvWF interaction



***Ex vivo* platelet string formation**



Anti-vWF Nanobody inhibits platelet string formation caused by ULvWF in plasma of TTP patients

Anti-VWF Nanobody = Caplacizumab

- Caplacizumab: (Cablivi®, Sanofi) has been approved for the treatment of acquired thrombotic thrombocytopenic purpura in the EU (August 2018) and USA (February 2019)

The NEW ENGLAND JOURNAL of MEDICINE

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

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†

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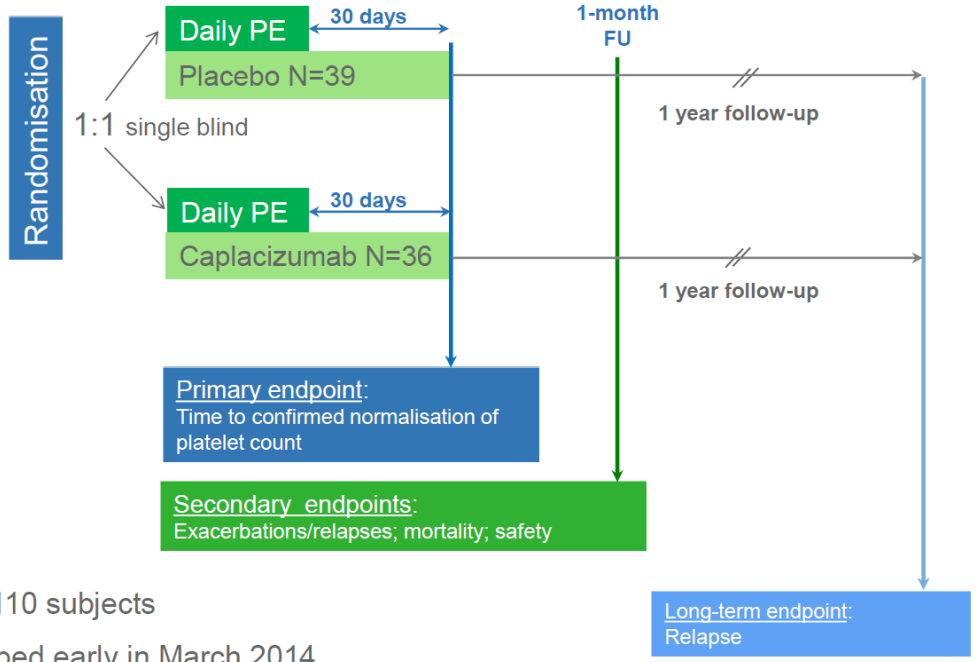
TITAN Study



Target – 110 subjects

Trial stopped early in March 2014

75 subjects enrolled over 3 years in 32 sites in Europe, US, Israel and Australia

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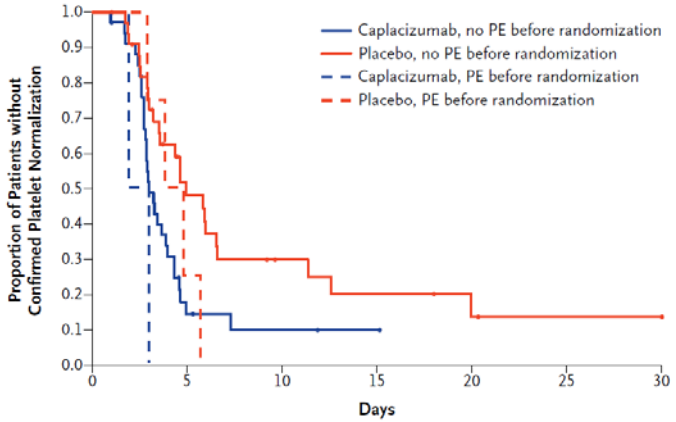
Normalization of platelet count

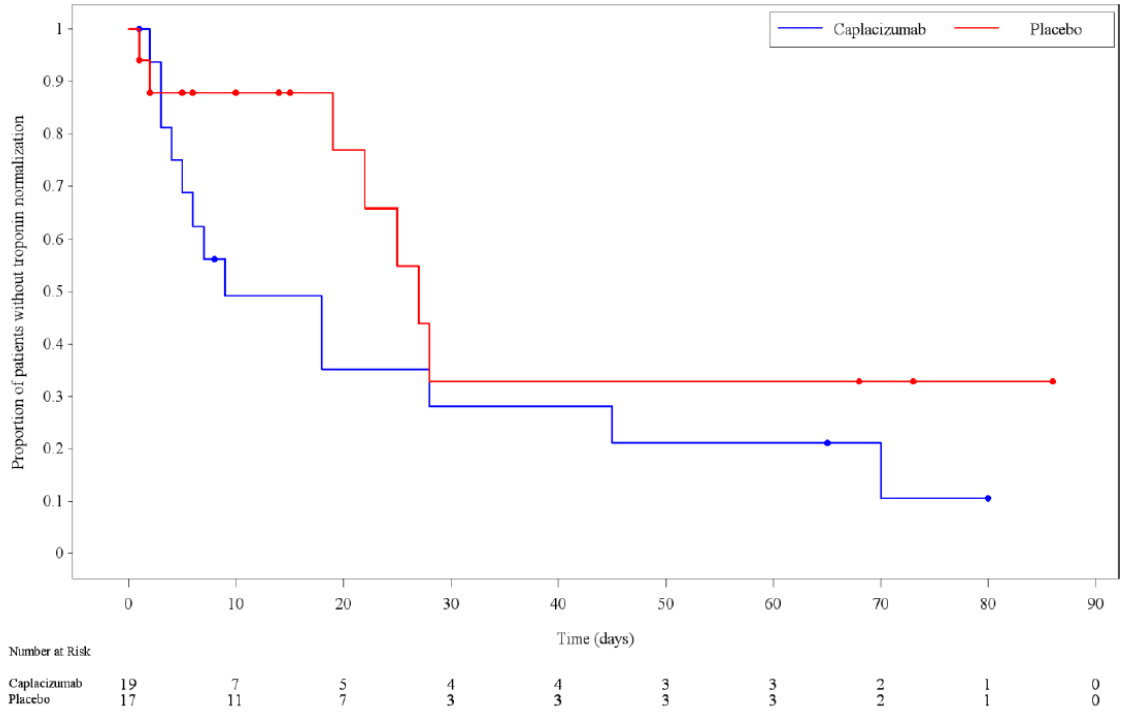
Time to response	Caplacizumab (N=36)	Placebo (N=39)
Median days (95% CI), NO prior PE	3.0 (2.7, 3.9)	4.9 (3.2, 6.6)
Median days (95% CI), one prior PE	2.4 (1.9, 3.0)	4.3 (2.9, 5.7)
Overall hazard rate ratio (95% CI) caplacizumab vs. placebo	2.2 (1.3, 3.8)	
Stratified log-rank test p-value	0.005	



No. at Risk							
Caplacizumab, no PE before randomization	34	4	2	1	0	0	0
Placebo, no PE before randomization	35	13	6	4	2	1	1
Caplacizumab, PE before randomization	2	0	0	0	0	0	0
Placebo, PE before randomization	4	1	0	0	0	0	0

Peyvandi F, *et al*. N Engl J Med 2016;374:511-22

Panel A: Time to first Troponin T or I normalization



Peyvandi F, *et al*. N Engl J Med 2016;374:511-22

Thromboembolic events and mortality

Table 1 Treatment-emergent major thromboembolic events and acquired thrombotic thrombocytopenic purpura (aTTP) exacerbations during the treatment period and overall aTTP-related mortality in the safety population of the phase II TITAN study

	Caplacizumab (N = 35)			Placebo (N = 37)		
	No. of events	No. of patients	% of patients	No. of events	No. of patients	% of patients
Major thromboembolic events (based on the SMQ, by preferred term)						
Acute myocardial infarction*	0	0	0	2	2	5.4
Pulmonary embolism	1	1	2.9	1	1	2.7
Deep vein thrombosis†	0	0	0	1	1	2.7
Venous thrombosis‡	0	0	0	1	1	2.7
Ischemic stroke§	0	0	0	1	1	2.7
Hemorrhagic stroke§	0	0	0	1	1	2.7
aTTP exacerbations (based on the SMQ, by preferred term)						
Thrombotic thrombocytopenic purpura¶	3	3	8.6	13	11	29.7
aTTP-related mortality						
Deaths related to TTP	0	0	0	2	2	5.4
Total	4	4**	11.4	22	16**	43.2

Peyvandi F, *et al*. J Thromb Haemost 2017; 15: 1448-52

Adverse Events and Serious Adverse Events

Adverse Event	Caplacizumab (N=35)	Placebo (N=37)	Total (N=72)
		no. of patients (%)	
Event related to study drug†	20 (57)	5 (14)	25 (35)
Event leading to discontinuation of study drug	4 (11)	2 (5)	6 (8)
Event leading to interruption of study drug	3 (9)	4 (11)	7 (10)
Event with death as outcome	0	2 (5)	2 (3)
Bleeding-related event	19 (54)	14 (38)	33 (46)
Immune-related event	17 (49)	12 (32)	29 (40)
Serious events			
Any	13 (37)	12 (32)	25 (35)

N Engl J Med 2019;380:335-46.

JANUARY 24, 2019

The NEW ENGLAND JOURNAL of MEDICINE

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*

METHODS

In this double-blind, controlled trial, we randomly assigned 145 patients with TTP to receive caplacizumab (10-mg intravenous loading bolus, followed by 10 mg daily subcutaneously) or placebo during plasma exchange and for 30 days thereafter. The primary outcome was the time to normalization of the platelet count, with discontinuation of daily plasma exchange within 5 days thereafter. Key secondary outcomes included a composite of TTP-related death, recurrence of TTP, or a thromboembolic event during the trial treatment period; recurrence of TTP at any time during the trial; refractory TTP; and normalization of organ-damage markers.

HERCULES Trial

RESULTS

The median time to normalization of the platelet count was shorter with caplacizumab than with placebo (2.69 days [95% confidence interval {CI}, 1.89 to 2.83] vs. 2.88 days [95% CI, 2.68 to 3.56], P=0.01), and patients who received caplacizumab were 1.55 times as likely to have a normalization of the platelet count as those who received placebo. The percentage of patients with a composite outcome event 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 no patients in the caplacizumab group and in three 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, which was reported in 65% of the patients in the caplacizumab group and in 48% in the placebo group. During the trial treatment period, three patients in the placebo group died. One patient in the caplacizumab group died from cerebral ischemia after the end of the treatment period.

CONCLUSIONS

Among patients with TTP, treatment with caplacizumab was associated with faster normalization of the platelet count; a lower incidence of a composite of TTP-related death, recurrence of TTP, or a thromboembolic event during the treatment period; and a lower rate of recurrence of TTP during the trial than placebo. (Funded by Ablynx; HERCULES ClinicalTrials.gov number, NCT02553317.)

Scully M, *et al*. N Eng J Med 2019;380:335-46

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Composite outcome:
- TTP-related death
- Recurrence of TTP
- Thromboembolic event
- Refractory TTP
- Normalization of organ-damage markers

Scully M, *et al*. N Eng J Med 2019;380:335-46

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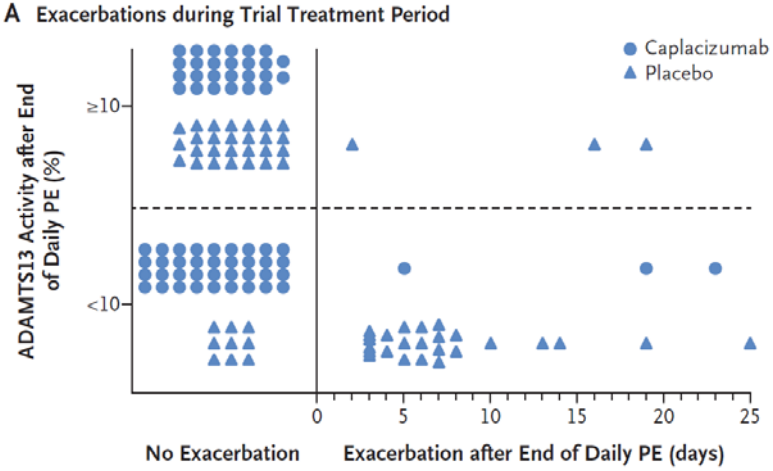
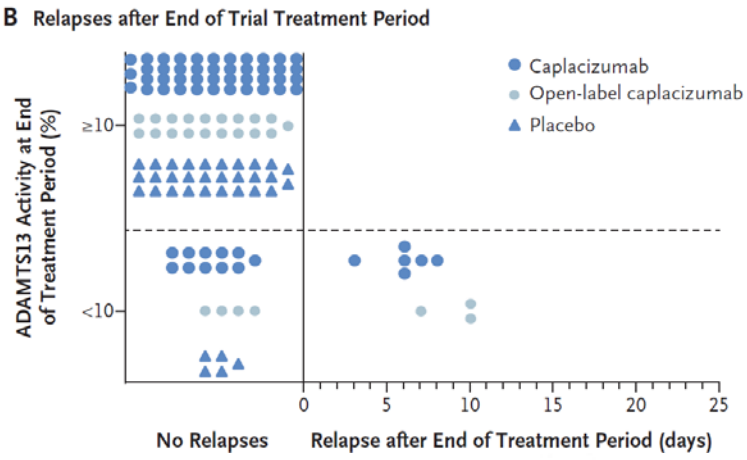
HERCULES Trial





120 patients, at the end of caplacizumab/placebo administration:-

29 (24%) ADAMTS13 activity < 10%

- 20 (69%) no relapses
- 9 (31%) relapsed

Scully M, *et al*. N Engl J Med 2019;380:335-46

Caplacizumab

- Does not remove the antibody blocking ADAMTS-13 activity
- Prevents platelets being consumed in microthrombi with ULvWF multimers:
  - faster normalization of platelets
  - reduction of tissue damage
- Platelet count or organ damage markers not anymore markers of disease activity
- We will have to find new ways of monitoring
- New paradigm in the treatment of acquired TTP

Mainstay for the treatment of aTTP

Future standard of care based on three pillars?

Daily PEX until confirmed platelet normalization

- Remove anti-ADAMTS13 autoantibodies and ULvWF.
- Replace functional ADAMTS13

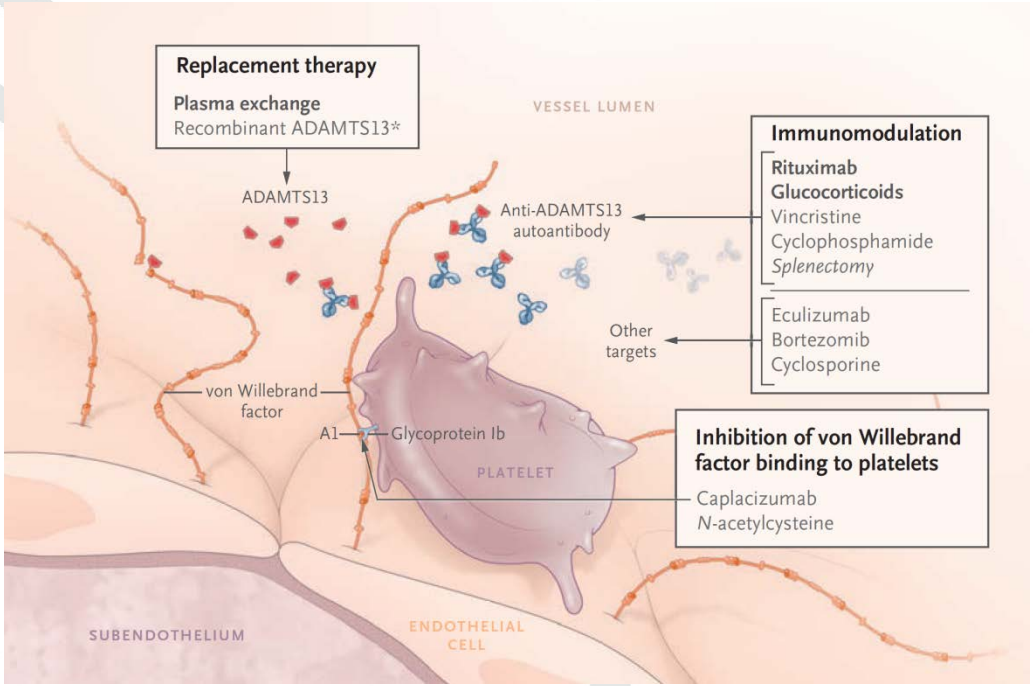
Immunosupression (Corticosteroids AND rituximab)

- Suppress autoantibody production

Caplacizumab

- Immediate blocking of binding of vWF to platelets
- Protection against microvascular thrombosis and organ damage
- Reduction in exacerbations
- Reduction in days and complications of PEX

Current and Emerging Therapeutic Approaches for aTTP



Veyradier A. N Engl J Med 2016;59-766

Cloning, expression, and functional characterization of the von Willebrand factor–cleaving protease (ADAMTS13)

Barbara Plaimauer, Klaus Zimmermann, Dirk Völkel, Gerhard Antoine, Randolf Kerschbaumer, Pegah Jenab, Miha Furlan, Helen Gerritsen, Bernhard Lämmle, Hans Peter Schwarz, and Friedrich Scheiflinger

Deficient von Willebrand factor (VWF) degradation has been associated with thrombotic thrombocytopenic purpura (TTP). In hereditary TTP, the specific VWF-cleaving protease (VWF-cp) is absent or functionally defective, whereas in the nonfamilial, acquired form of TTP, an autoantibody inhibiting VWF-cp activity is found transiently in most patients. The gene encoding for VWF-cp has recently been identified as a member of the metalloprotease family and designated *ADAMTS13,* but the functional activity of the ADAMTS13 gene product has not been verified. To establish the functional activity of recombinant VWF-cp, we cloned the complete cDNA sequence in a eukaryotic expression vector and transiently expressed the encoded recombinant ADAMTS13 in HEK 293 cells. The expressed protein degraded VWF multimers and proteolytically cleaved VWF to the same fragments as those generated by plasma VWF-cp. Furthermore, recombinant ADAMTS13-mediated degradation of VWF multimers was entirely inhibited in the presence of plasma from a patient with acquired TTP. These data show that ADAMTS13 is responsible for the physiologic proteolytic degradation of VWF multimers. (Blood. 2002;100:3626-3632)

UNIVERSITAT DE BARCELONA

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Plenary Paper

blood

CLINICAL TRIALS AND OBSERVATIONS

Recombinant ADAMTS-13: first-in-human pharmacokinetics and safety in congenital thrombotic thrombocytopenic purpura

Marie Scully,[1] Paul Knöbl,[2] Karim Kentouche,[3] Lawrence Rice,[4] Jerzy Windyga,[5] Reinhard Schneppenheim,[6] Johanna A. Kremer Hovinga,[7] Michiko Kajiwara,[8] Yoshihiro Fujimura,[9] Caterina Maggiore,[10] Jennifer Doralt,[11] Christopher Hibbard,[12] Leah Martell,[12] and Bruce Ewenstein[12]

[1]Department of Haematology and Cardiometabolic BRC, University College London Hospitals/University College London, London, United Kingdom; [2]Division of Hematology and Hemostasis, Department of Medicine 1, Medical University of Vienna, Austria; [3]Jena University Hospital, Jena, Germany; [4]Department of Medicine, Houston Methodist Hospital, Weill Cornell Medical College, Houston, TX; [5]Department Disorders of Hemostasis and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [6]Department of Pediatric Hematology and Oncology, Universitaetsklinikum Hamburg-Eppendorf, Hamburg, Germany; [7]Inselspital, University Hospital Bern, Bern, Switzerland; [8]Tokyo Medical and Dental University Hospital Faculty of Medicine, Tokyo, Japan; [9]Nara Medical University, Nara, Japan; [10]Quintiles, Milan, Italy; [11]Shire, Vienna, Austria; and [12]Shire, Cambridge, MA

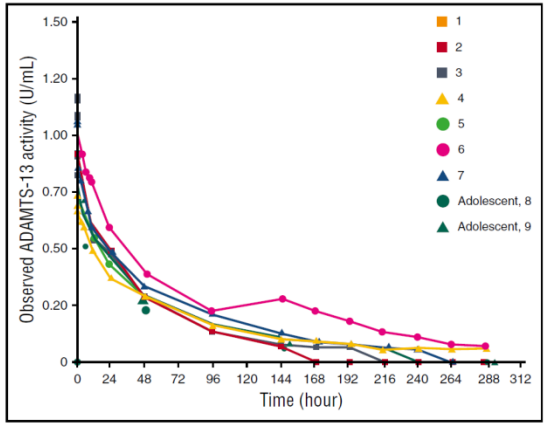

Figure 2. Observed ADAMTS-13 activity over time. ADAMTS-13 activity in plasma was measured at baseline and at times up to 288 hours, using the FRETS-VWF73 assay after a 40 U/kg administration of BAX 930.

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ClinicalTrials.gov

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Save this study

Study of rADAMTS-13 (SHP655) in the Treatment of Participants With Acquired Thrombotic Thrombocytopenic Purpura (aTTP) (SOAR-HI)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03922308

Recruitment Status : Not yet recruiting
First Posted : April 19, 2019
Last Update Posted : May 24, 2019

See Contacts and Locations

Sponsor:
Shire

Information provided by (Responsible Party):

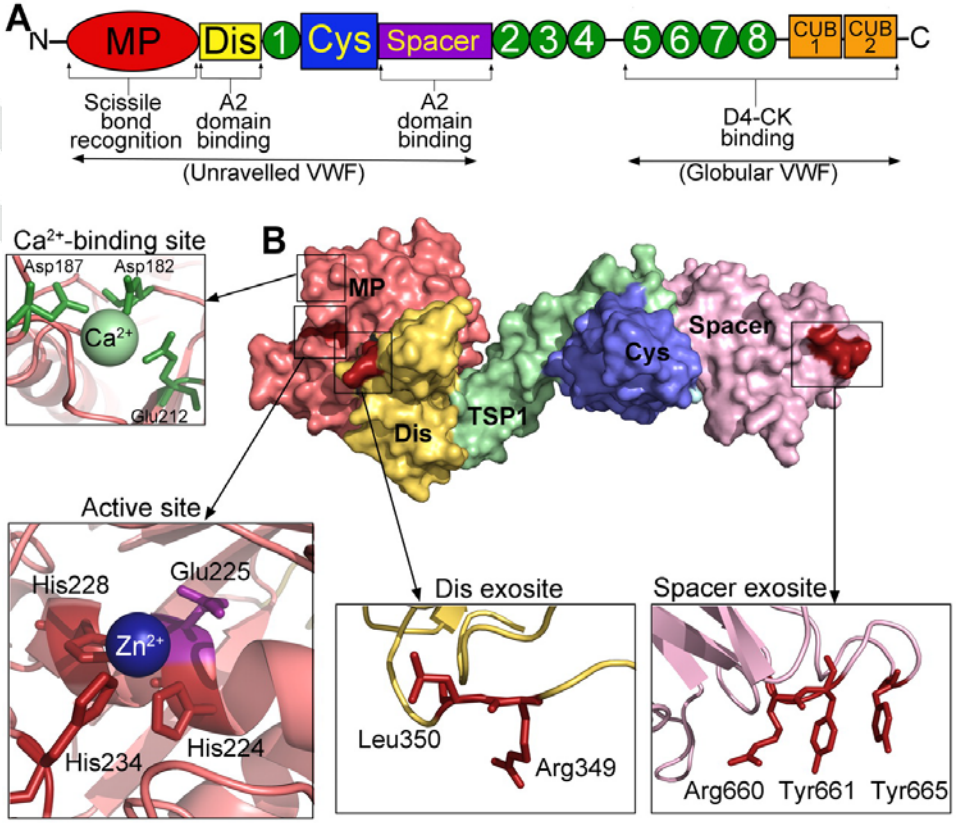
Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	30 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-blind Study in Patients With Acquired Thrombotic Thrombocytopenic Purpura (aTTP) to Evaluate the Pharmacokinetics,Safety and Efficacy of rADAMTS-13 (SHP655) Administered in Addition to Standard Of Care (SoC) Treatment
Estimated Study Start Date :	June 9, 2019
Estimated Primary Completion Date :	December 30, 2020
Estimated Study Completion Date :	December 30, 2020

Conclusions

- In the last 20 years huge advances in the knowledge of the pathophysiology of acquired TTP have occured
- Accordingly the therapeutic approach have changed significantly
- New drugs will change the way how we manage patients with the condition reducing even further the morbidity and mortality of the disease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A2 domain binding
A2 domain binding
D4-CK binding
(Unravelled VWF)
(Globular VWF)
Ca2+-binding site
Asp187
Asp182
Ca2+
Glu212
B
MP
Spacer
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Dis
Active site
His228
Glu225
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His234
His224
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Leu350
Arg349
Spacer exosite
Arg660
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