Current treatment in TTP

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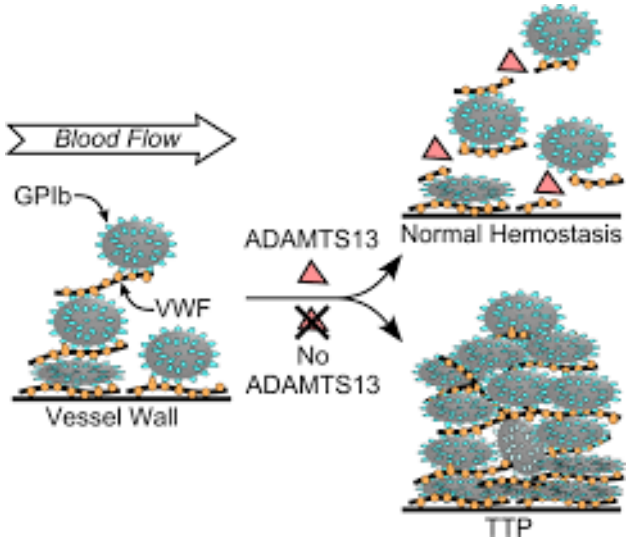
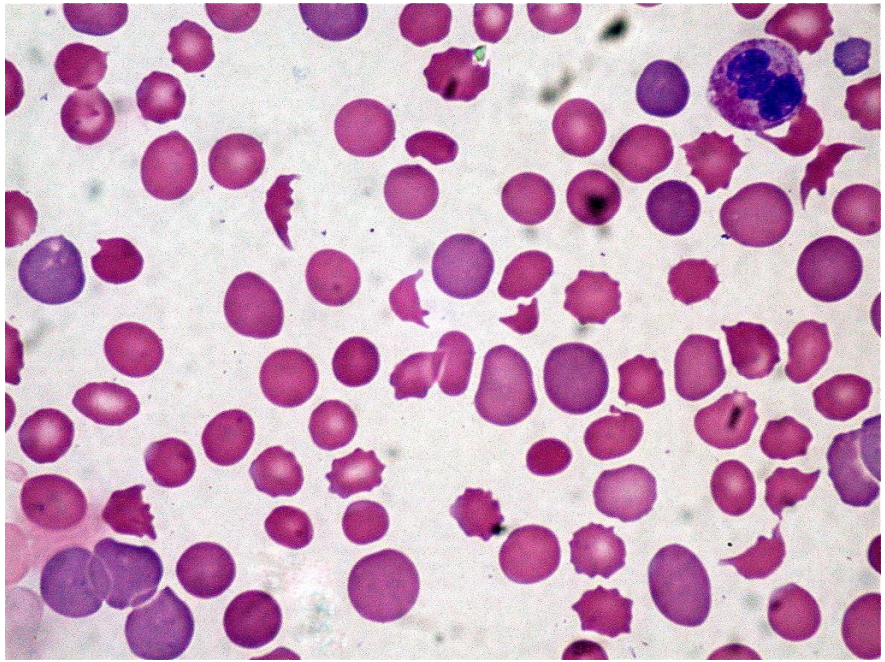
November 2019

Thrombotic thrombocytopenic purpura

- Thrombotic microangiopathy causing widespread microthrombi formation leading to organ failure and death
- Rare; incidence 6 per million
- Untreated mortality 90%;
  - 50% deaths occur within 24h of presentation
  - 1 in 6 will have refractory disease
- Acquired or congenital

- NEJM video


Blood Flow
GPIb
VWF
Vessel Wall
ADAMTS13
No
ADAMTS13
Normal Hemostasis
TTP



Pathogenesis of acquired TTP

- Von Willebrand factor released as large proteins from blood vessel walls
- vWF aggregates platelets
- ADAMTS13 cleaves vWF into shorter multimers

- In TTP, antibodies to ADAMTS13 → reduced levels → ultralarge vWF multimers → unregulated platelet aggregation →
  - Widespread microthrombi
  - Microangiopathic haemolytic anaemia
  - Thrombocytopenia

Presentation of TTP

- Thrombocytopenia
  - NO PLATELET TRANSFUSION!
- Fragments on blood film (MAHA)
- Fever
- Renal impairment (mild)
- Neurological symptoms
- Cardiac impairment

Multisystem disorder with high mortality

Treatment of TTP

1. Removal of the antibody
2. Replenishment of ADAMTS13

- Plasma exchange within 4 hours (1.5 volumes/day initially)
- Steroids
- Rituximab (neuro/cardiac involvement)
- Aspirin and LMWH when platelets >50 $x10^9$/L
- Folic acid

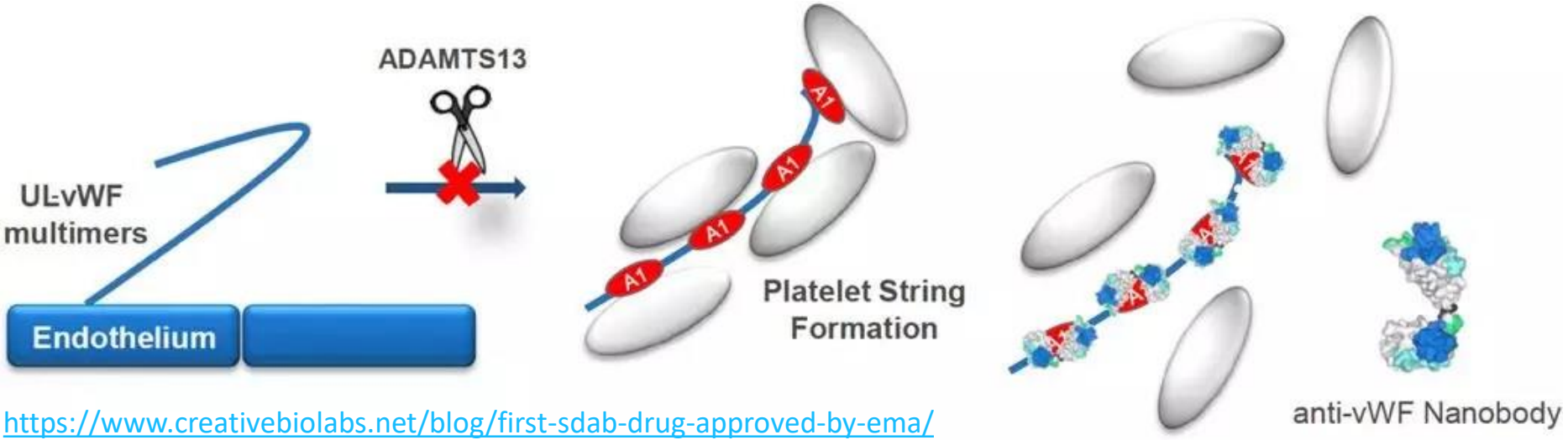
Survival now >80%

Plasma for TTP treatment

- Octaplas used historically
- Evidence based
- Fewer transfusion reactions
- SaBTO removed the recommendation for Octaplas March 2019 based on vCJD risk alone
- TTP guidelines will continue to recommend Octaplas

Caplacizumab

- anti–von Willebrand factor humanized single-variable-domain immunoglobulin
- targets the A1 domain of von Willebrand factor, preventing interaction with the platelet glycoprotein Ib-IX-V receptor



https://www.creativebiolabs.net/blog/first-sdab-drug-approved-by-ema/

TITAN study (NEJM, 2016)

ORIGINAL ARTICLE

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., et al., for the TITAN Investigators†

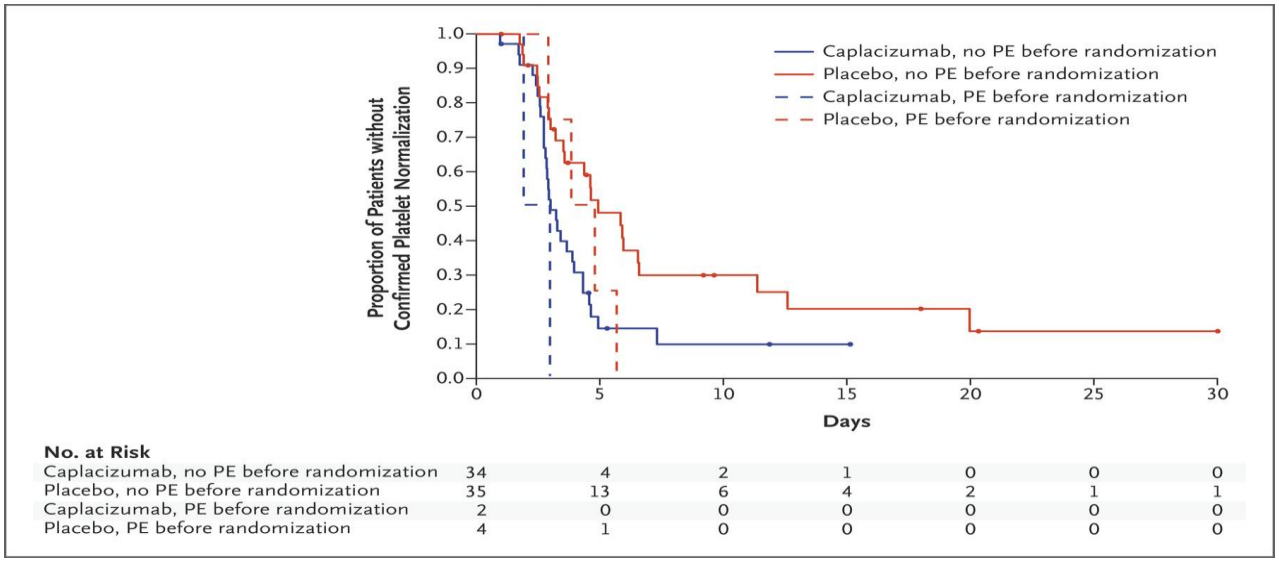
- Multicentre, single-blind, randomised, placebo-controlled
- Adults with (new or relapsed) TTP requiring PEx and with no bleeding
- Standard care + caplacizumab or placebo
- Capla 10mg IV 6h to 15 mins prior to first exchange
- Then SC OD within 30 mins of the end of the exchange
- Daily until 30 days after the last exchange (max 90d)

Primary outcome (“event ratio”)

In patients who had not had PEx prior to randomisation (n=69), median time to a response was

3.0 days (95% confidence interval [CI], 2.7 to 3.9) - caplacizumab

4.9 days (95% CI, 3.2 to 6.6) - placebo



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

Table 2. Primary and Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Caplacizumab (N=36)	Placebo (N=39)
Primary end point		
Time to response: caplacizumab vs. placebo		
Event rate ratio (95% CI)*	2.20 (1.28–3.78)	
P value†	0.005	
Patients with no PE before randomization		
Median time to response (95% CI) — days	3.0 (2.7–3.9)	4.9 (3.2–6.6)
Confirmed response — no. (%)	29 (81)	24 (62)
Data censored at 30 days — no. (%)	5 (14)	11 (28)
Patients with one PE before randomization		
Median time to response (95% CI) — days	2.4 (1.9–3.0)	4.3 (2.9–5.7)
Confirmed response — no. (%)	2 (6)	4 (10)
Data censored at 30 days — no. (%)	0	0
Secondary end points		
Exacerbation of TTP — no. (%)‡	3 (8)	11 (28)
Relapse — no. (%)		
During 1-mo follow-up period	8 (22)	0
During 12-mo follow-up period§	11 (31)	3 (8)
Complete remission after initial daily PE — no. (%)¶	29 (81)	18 (46)
Mean no. of PE days (range)		
During daily PE period	5.9 (3–15)	7.9 (2–35)
During overall study-drug treatment period	7.7 (3–21)	11.7 (2–43)
During the first 30 days of follow-up	10.2 (4–29)	11.7 (2–43)

* The event rate ratio (i.e., the hazard ratio) is based on a stratified Cox proportional-hazards regression model with one PE session before randomization (yes or no) as a covariate.
† The P value, from a one-sided log-rank test of superiority at a 2.5% significance level, is based on an analysis stratified for the presence or absence of one PE session before randomization. An observation was censored if it did not meet the defined interval of 30 days after the first study-drug administration.
‡ An exacerbation was defined as an episode of thrombocytopenia that occurred between 1 and 30 days after the last daily PE session and required reinitiation of daily PE treatment.
§ Relapse was defined as a new episode of thrombocytopenia, and a new episode was defined as one that occurred more than 30 days after the last daily PE session.
¶ Complete remission after the initial course of daily PE (i.e., plasma exchange given for the presenting acquired TTP episode) was defined as a confirmed normalization of the platelet count (i.e., confirmed response) and an absence of exacerbations.

- 8 patients in the capla group had relapse within 30d of stopping (7 within 10d);
- All patients who relapsed within 10d had low ADAMTS13 levels during treatment and shortly before stopping
- 2 deaths: both placebo (TTP; ICH)

- More relapses
- Troponin and other biomarkers quicker to normalise with caplacizumab
- Bleeding risk?
  - Ricof drops to about 20%
- Subsequent paper in JTH showing reducing risk of major thromboembolic events with caplacizumab

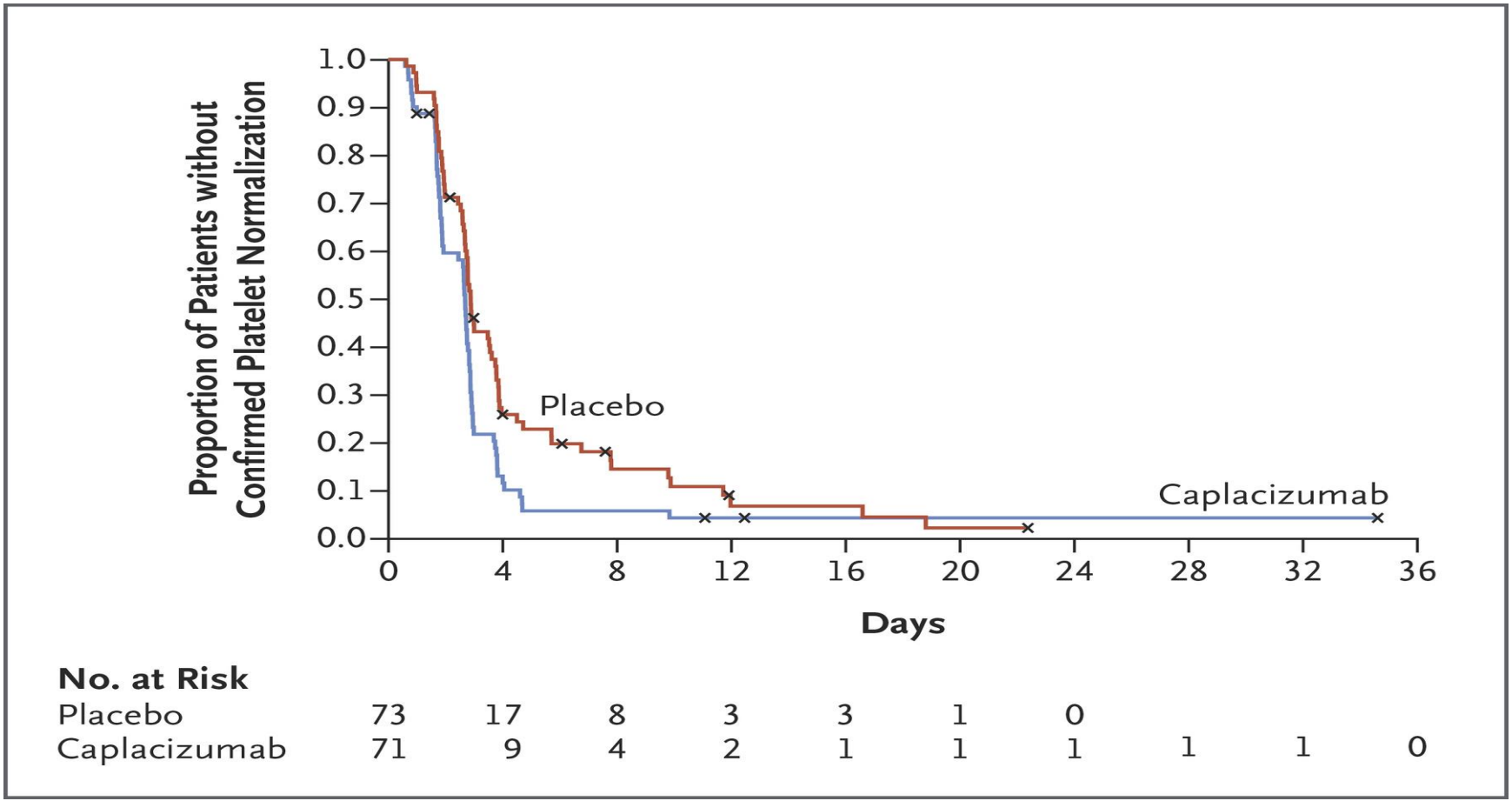
HERCULES trial (NEJM, 2019)

ORIGINAL ARTICLE

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura

Marie Scully, M.D., Spero R. Cataland, M.D., Flora Peyvandi, M.D., Ph.D., Paul Coppo, M.D., Ph.D., Paul Knöbl, M.D., Johanna A. Kremer Hovinga, M.D., Ara Metjian, M.D., Javier de la Rubia, M.D., Katerina Pavenski, M.D., Filip Callewaert, Ph.D., Debjit Biswas, Ph.D., Hilde De Winter, M.D., et al., for the HERCULES Investigators*

- Similar trial design but capla continued until ADAMTS13 levels normalised, up to an additional 28d i.e. 58d post end of PEx
- Some children (but excluded if congenital)
- FU 28d after last dose


Proportion of Patients without Confirmed Platelet Normalization
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Placebo
Caplacizumab
0
4
8
12
16
20
24
28
32
36
Days
No. at Risk
Placebo 73 17 8 3 3 1 0
Caplacizumab 71 9 4 2 1 1 1 1 1 0

- 1.55x as likely to normalise platelets at any given time in caplacizumab group
- Composite outcome of TTP-related death, recurrence of TTP, or a major thromboembolic event
  - 9 patients (12%) in the caplacizumab group
  - 36 patients (49%) in the placebo group.

  - 74% lower incidence with caplacizumab than with placebo ($P<0.001$)

Table 2. Primary and Secondary Efficacy Outcomes in the Intention-to-Treat Population.

Outcome	Caplacizumab (N = 72)	Placebo (N = 73)	P Value
Primary outcome			
Time to normalization of platelet count			
25th Percentile (95% CI) — days	1.75 (1.65–1.87)	1.94 (1.70–2.64)	
50th Percentile (95% CI) — days	2.69 (1.89–2.83)	2.88 (2.68–3.56)	
75th Percentile (95% CI) — days	2.95 (2.85–3.81)	4.50 (3.78–7.79)	
Rate ratio for normalization of platelet count, caplacizumab vs. placebo (95% CI)*	1.55 (1.09–2.19)		0.01
Key secondary outcomes			
Composite of TTP-related death, recurrence of TTP, or major thromboembolic event during the double-blind treatment period — no. (%)	9 (12)	36 (49)	<0.001
TTP-related death	0	3 (4)	
Recurrence of TTP: exacerbation†	3 (4)	28 (38)	
Major thromboembolic event	6 (8)	6 (8)	
Recurrence of TTP at any time during the trial — no. (%)†	9 (12)	28 (38)	<0.001
During the double-blind treatment period: exacerbation	3 (4)	28 (38)	
During the follow-up period: relapse‡	6 (8)	0	
Refractory TTP — no. (%)§	0	3 (4)	0.06
Median time to normalization of organ-damage markers (95% CI) — days	2.86 (1.93–3.86)	3.36 (1.88–7.71)	

Other secondary outcomes¶		
Number of days of plasma exchange		
Mean (95% CI)	5.8 (4.8–6.8)	9.4 (7.8–11.0)
Median (range)	5.0 (1.0–35.0)	7.0 (3.0–46.0)
Volume of plasma exchanged — liters		
Mean (95% CI)	21.3 (18.1–24.6)	35.9 (27.6–44.2)
Median (range)	18.1 (5.3–102.2)	26.9 (4.0–254.0)
No. of days of hospitalization		
Mean (95% CI)	9.9 (8.5–11.3)	14.4 (12.0–16.9)
Median (range)	9.0 (2.0–37.0)	12.0 (4.0–53.0)
Patients admitted to the intensive care unit — no. (%)‖	28 (39)	27 (37)
No. of days in the intensive care unit		
Mean (95% CI)	3.4 (2.6–4.2)	9.7 (5.3–14.1)
Median (range)	3.0 (1.0–10.0)	5.0 (1.0–47.0)

Safety

- Deaths: 1 capla; 3 placebo – all TTP related
- Adverse events 32% capla; 16% placebo
- Bleeding **64.8% vs 47.9%**
  - Gingival bleeding, epistaxis
  - Severe in 3 capla, 1 placebo

Summary

- Caplacizumab is a monoclonal antibody directed towards the A1 domain of vWF
- Given with standard treatments for TTP it reduces time to normalisation of platelet count, reduced transfusion and ITU/hospital LOS
- There is an increased bleeding risk
- Risk of relapse is high if the drug is stopped while ADAMTS13 levels are still <10%
- It is licensed by the EMA; NICE approval awaited