ITP

…..una lunga storia…..

Epidemiologia dell'ITP primaria: incidenza

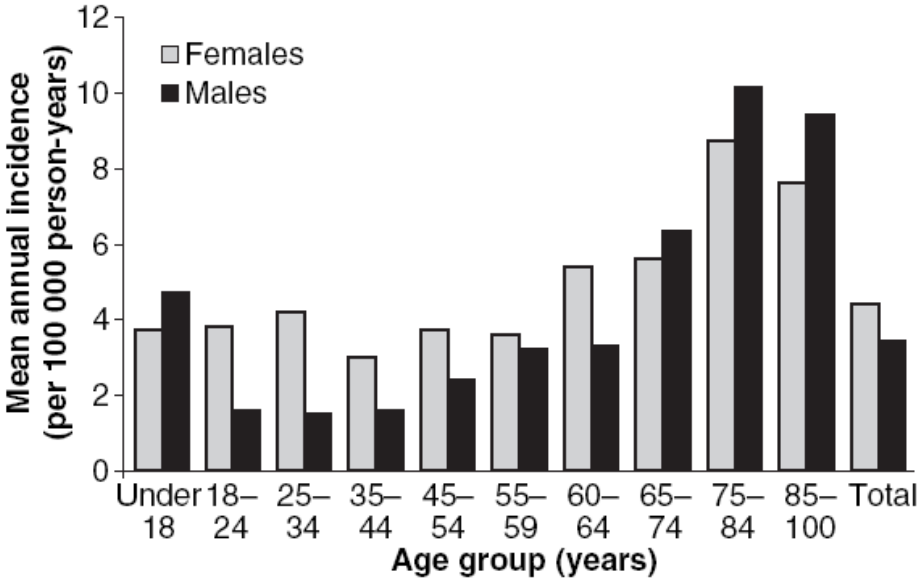
Study	Country	Methodology	Accrual years	Sample size	Reported results/ 10^5 adults/year	Age of subjects	Inclusion criteria
1[20]	Denmark	Retrospective chart review	1973–1995	221	2.6	16 years and older	ICD-8-CM code or ICD-10 CM code representing thrombocytopenia, validated by chart review and platelet count less than 100,000/μL
				NR	2.3		ICD-8-CM code or ICD-10 CM code representing thrombocytopenia, validated by chart review and platelet count less than 50,000/μL
			1985–1995	NR	3.3		ICD-8-CM code or ICD-10 CM code representing thrombocytopenia, validated by chart review and platelet count less than 100,000/μL
				NR	2.7		ICD-8-CM code or ICD-10 CM code representing thrombocytopenia, validated by chart review and platelet count less than 50,000/μL
2[21]	United Kingdom	Prospective registration	1993–1999	245	1.6	16 years and older	At least one platelet count less than 50,000/μL and confirmatory bone marrow aspirate and biopsy
3[22]	United Kingdom	Retrospective secondary analysis	1992–2005	840	3.9	18 years and older	Read or Oxford Medical Information System diagnosis code representing thrombocytopenia in the General Practice Research Database
Combined incidence estimate (children and adults)							
1[23]	Sweden	Retrospective chart review	1964–1968	152	2.5	All ages	Hospital discharge ICD code 296.03 and platelet count less than 100,000/μL validated by chart review
2[24]	United Kingdom	Retrospective secondary analysis	1990–2005	1145	3.9	All ages	Read or Oxford Medical Information System diagnosis code representing thrombocytopenia in the General Practice Research Database

1.6-3.9x100.000 adults/yrs

[a] NR, not reported.

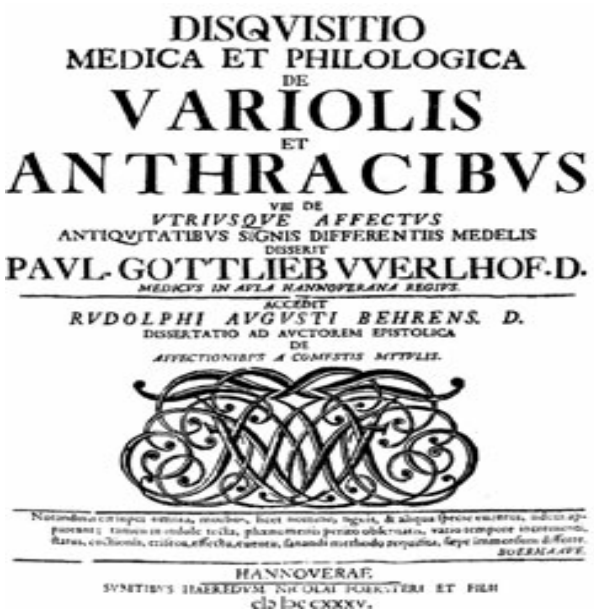
Epidemiologia dell'ITP primaria: incidenza

1145 patients; 652 women, 57% (PLT < 150 x 10^9/L)



Schoonen WM et al, *Br J Haematol* 2009

In 1735, the German physician and poet Paul Gottlieb Werlhof (1699–1767) provided the classic clinical description of ITP, calling it ‘morbus maculosus haemorrhagicus’ (Fig 2). He reported the case of a 16-year-old girl with cutaneous and mucosal bleeding that occurred after an infectious disease (Werlhof, 1735). The girl bled from her nose and mouth and vomited ‘very thick, extremely black blood. Immediately there appeared about the neck and on the arms, spots partly black, partly violaceous or purple…’. This condition was subsequently named after Werlhof, and the eponym is sometimes still used instead of ITP.


DISQVISITIO
MEDICA ET PHILOLOGICA
DE
VARIOLIS
ET
ANTHRACIBVS
VEL DE
VTRIVSQVE AFFECTVS
ANTIQVITATIBVS SIGNIS DIFFERENTIIS MEDELIS
DISSERIT
PAVL. GOTTLIEB VVERLHOF. D.
MEDICVS IN AVLA HANNOVERANA REGIVS.
ACCEDIT
RVDOLPHI AVGVSTI BEHRENS. D.
DISSERTATIO AD AVCTOREM EPISTOLICA
DE
AFFECTIONIBVS A COMESTIS MYTILIS.
HANNOVERAE.
SVMTIBVS HAEREDVM NICOLAI FOERSTERI ET FILII
cIↃ IↃc CXXXV.

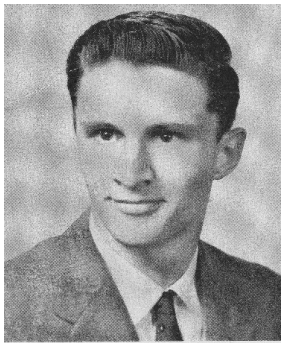
… … … … … … 1916

In 1916 a medical student in Prague, Paul Kaznelson (Fig 5), challenged Frank's idea (Berl Klin Wochenschr, 1915) and proposed that, in analogy with haemolytic anaemia, essential thrombocytopenia resulted from increased platelet destruction in the spleen. Kaznelson convinced his tutor, Professor Doktor Schloffer (Fig 5), to perform a splenectomy in a 36-year-old woman with a history consistent with our current definition of chronic ITP. The patient for most of her life had suffered from easy bruising, frequent epistaxis and heavy menstrual bleeding. The platelet count was $2x10^9$/L prior to splenectomy and rose to $500x10^9$/L within 4 weeks from surgery with complete resolution of the purpura (Kaznelson, 1916). However, in the next two cases only temporary increases of the platelet count were observed (Kaznelson, 1919).

… … … … … … 1950

ACTH

Cortisone



MISCELLANEOUS

Demonstration of a Thrombocytopenic Factor in the Blood of Patients With Thrombocytopenic Purpura. **W. J. Harrington, M. S. Minnich, J. W. Hollingsworth,** and **C. V. Moore.** J. Lab. & Clin. Med. 38: 1, July, 1951.

A thrombocytopenic factor has been demonstrated in the whole blood and plasma from eight of ten patients with idiopathic thrombocytopenic purpura and from one of three subjects with secondary thrombocytopenia. Administration of 500 c.c. of citrated whole blood or its plasma equivalent from these nine patients caused a prompt, and often dramatic, decrease in the platelet counts of nonthrombocytopenic recipients. The thrombocytopenic effect persisted for five to seven days and, when severe, was associated with a prolonged bleeding time and decreased prothrombin consumption. The factor was stable for at least nine days at 5° C., and for at least eight days at 25° C. In the one plasma fractionation that has so far been done, the thrombocytopenic factor was found in the globulin fraction. Two patients who were demonstrated to have the platelet-reducing factor prior to splenectomy still had the factor present after platelet counts had returned to normal following removal of the spleen.

Jack Bloom.

Idiopathic Thrombocytopenic Purpura
Some Ideas on Its Pathogenesis and Treatment

WILLIAM DÀMESHEK and MARIO STEFANINI

Med Clin North Am 1953

DEFINITION AND DIFFERENTIAL DIAGNOSIS

Idiopathic thrombocytopenic purpura has three features which are all-important from the standpoint of differential diagnosis and definition:

1. The platelet count is low but there is no apparent abnormality of the red cells or leukocytes.
2. The spleen is not ordinarily palpable, or if so, just slightly.
3. The bone marrow contains abundant megakaryocytes.

It may be defined as a disorder of obscure causation characterized by an acute or chronic reduetion in the blood platelet count, in the presence of otherwise essentially normal blood counts, a normal sized spleen, and a marrow containing normal or increased numbers of megakaryocytes. Occasionai cases of bone marrow disease either following chemieal or x-ray exposure or even in leukemia may show thrombocytopenia as the first hematologìc abnormality. Thus it is always essential when con-fronted with a patient showing thrombocytopenia to note the various features of the blood count and to study an aspirate of the bone marrow. In bone marrow disorders of various types whether due to hypoplastic anemia, leukemia, leukosarcoma or metastatic carcinoma, the mega-karyoeytes are greatly reduced or are lacking compìetely. In idiopathic thrombocytopenic purpura on the other hand, these gìant cells are usually increased in number, despite the paucity of the platelets'in the blood.[1] Their platelet production, however, as judged by studies either with regular staining methods or with phase microscopy, is greatly reduced. Obviously, there is a great difference in the significanee of a bone marrow depleted of megakaryocytes and one in which the megakaryo-cytes are numerous, albeit unproductive. Thus, thrombocytopenia can be divided into amegakaryocytic (secondary) and megakaryocytic forms.

… … … … … … 1955

Prednisone

THE JOURNAL

OF THE

American Medical Association

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TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) WITH PREDNISONE

William Dameshek, M.D., Fernando Rubio Jr., M.D.
John P. Mahoney, M.D., W. Harrison Reeves, M.D.
and
Leonard A. Burgin, M.D., Boston

La patogenesi della ITP

• **Nel 1965 Shulman con altri studi di infusione di plasma di pazienti con ITP, dimostrò che il fattore plasmatico distruggeva sia le piastrine autologhe che quelle omologhe**

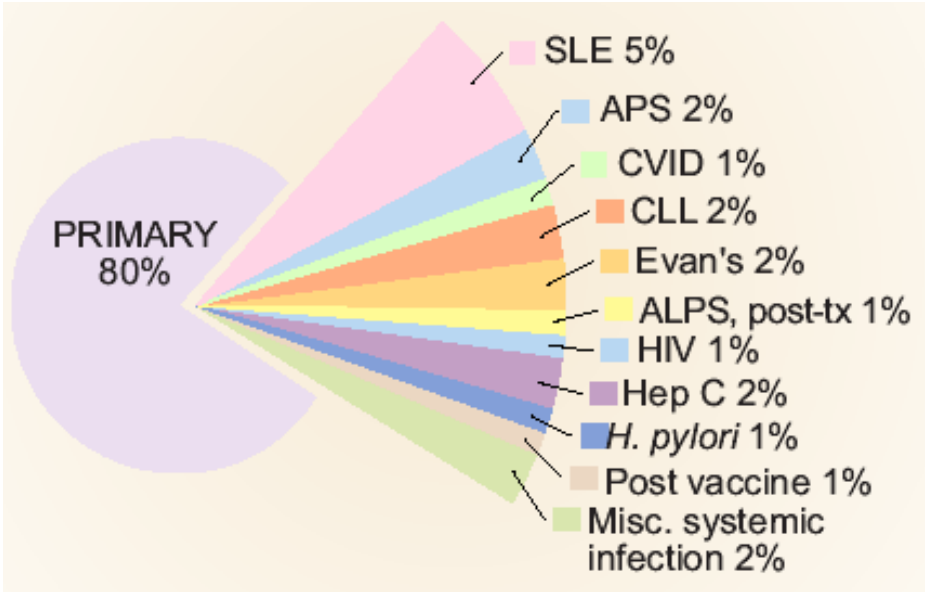
• **L'effetto era dose-dipendente e meno evidente in pazienti splenectomizzati, con emolisi cronica e precedentemente trattati con steroidi**

• **Il fattore plasmatico poteva essere captato dalle piastrine ed era riscontrabile nella frazione plasmatica IgG-arricchita (NY Acad Sci, 1965; Trans Assoc Am Physicians, 1965)**

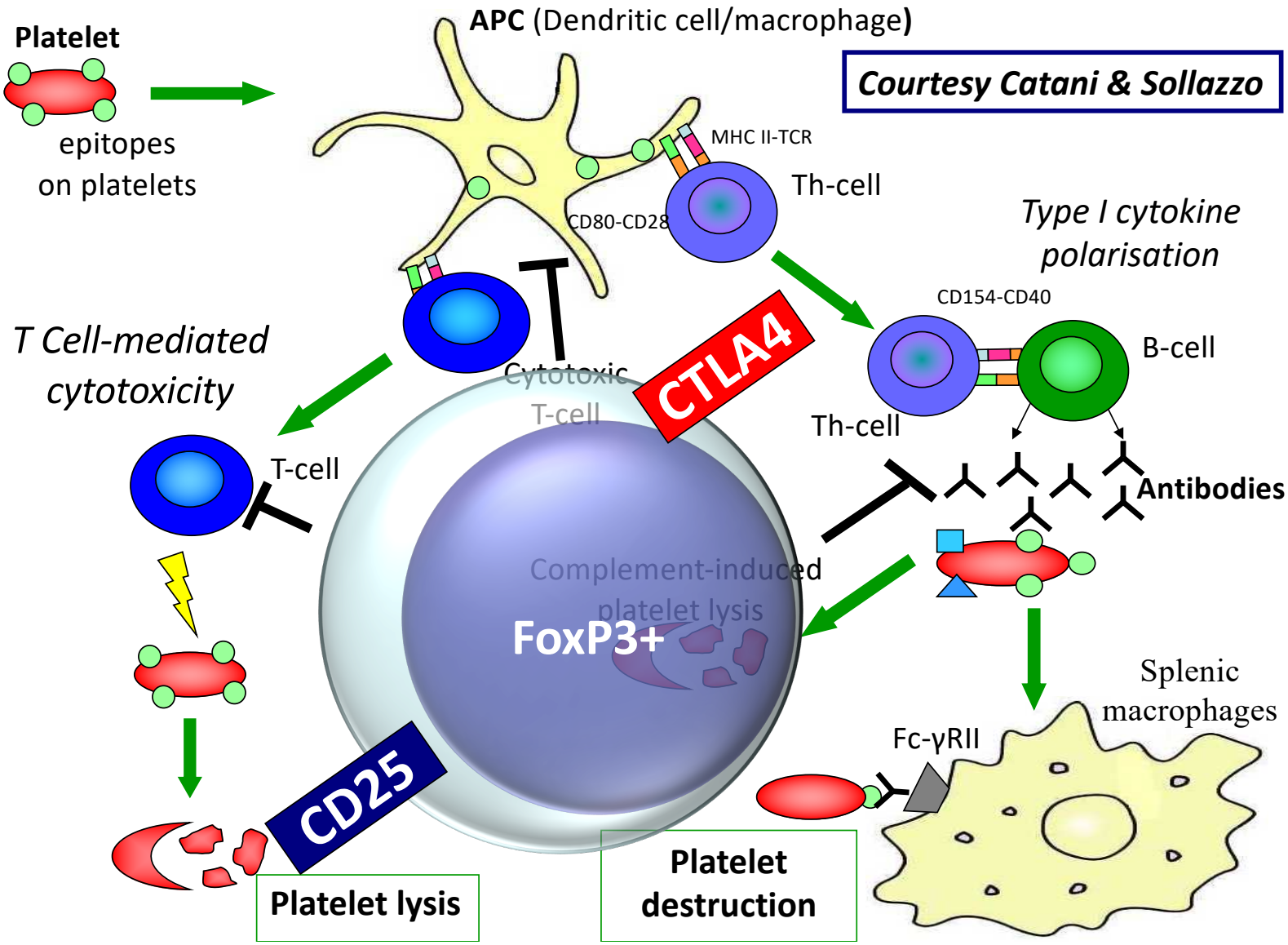
Fattore plasmatico = Anticorpo antipiastrine

ITP è una patologia autoimmune

La causa della risposta autoimmune nella ITP non è nota e probabilmente differisce tra i pazienti



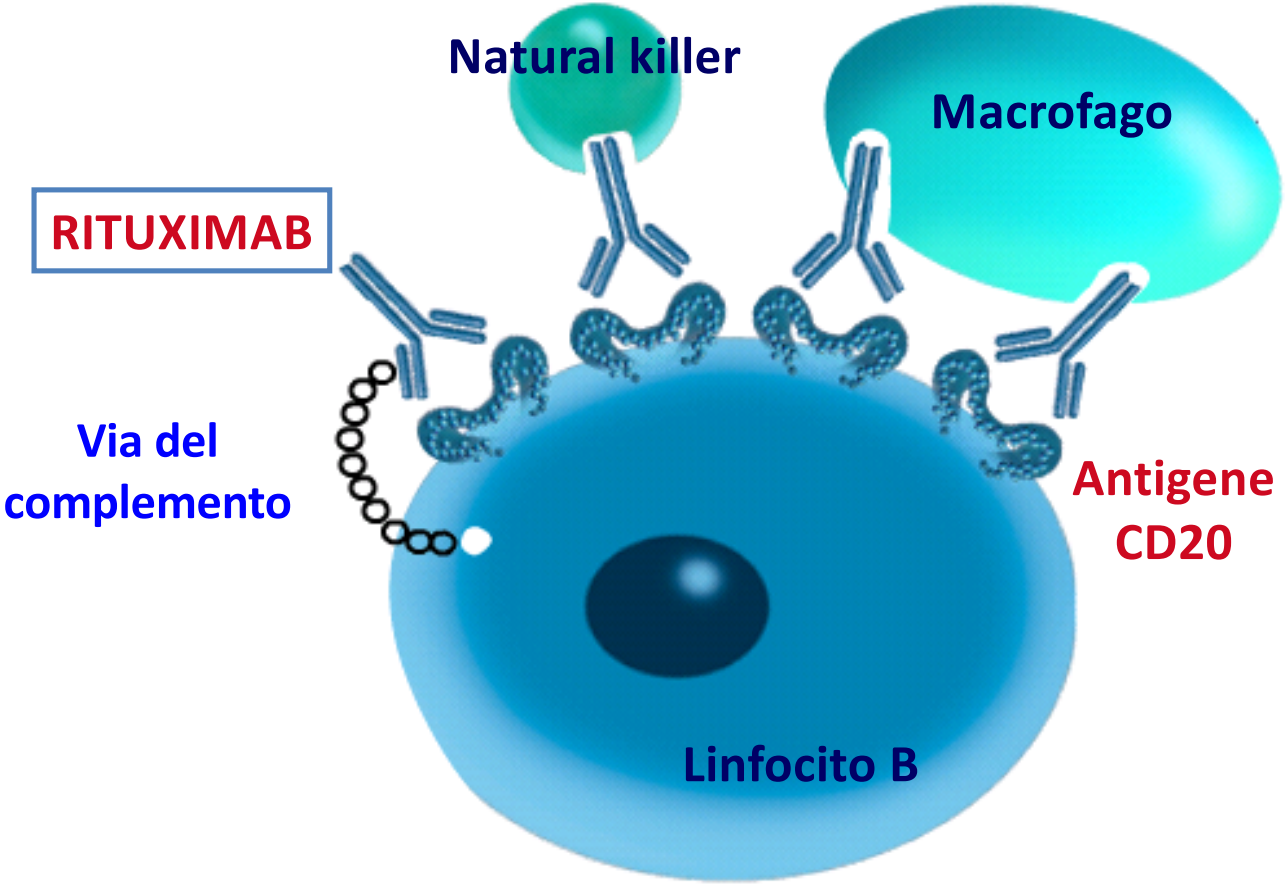
Cines DB, Blood 2009


Platelet
epitopes
on platelets
APC (Dendritic cell/macrophage)
Courtesy Catani & Sollazzo
MHC II-TCR
Th-cell
CD80-CD28
Type I cytokine
polarisation
CD154-CD40
B-cell
Th-cell
Antibodies
T Cell-mediated
cytotoxicity
Cytotoxic
T-cell
CTLA4
T-cell
Complement-induced
platelet lysis
FoxP3+
Splenic
macrophages
Fc-γRII
CD25
Platelet lysis
Platelet
destruction

……..anni 2000…..

Rituximab: meccanismo d'azione

Attività citotossica complemento e cellulo - mediata



DEPLETION OF B LYMPHOCYTES WITH RITUXIMAB

McLaughlin P et al. *J Clin Oncol*. 1998;16:2825.

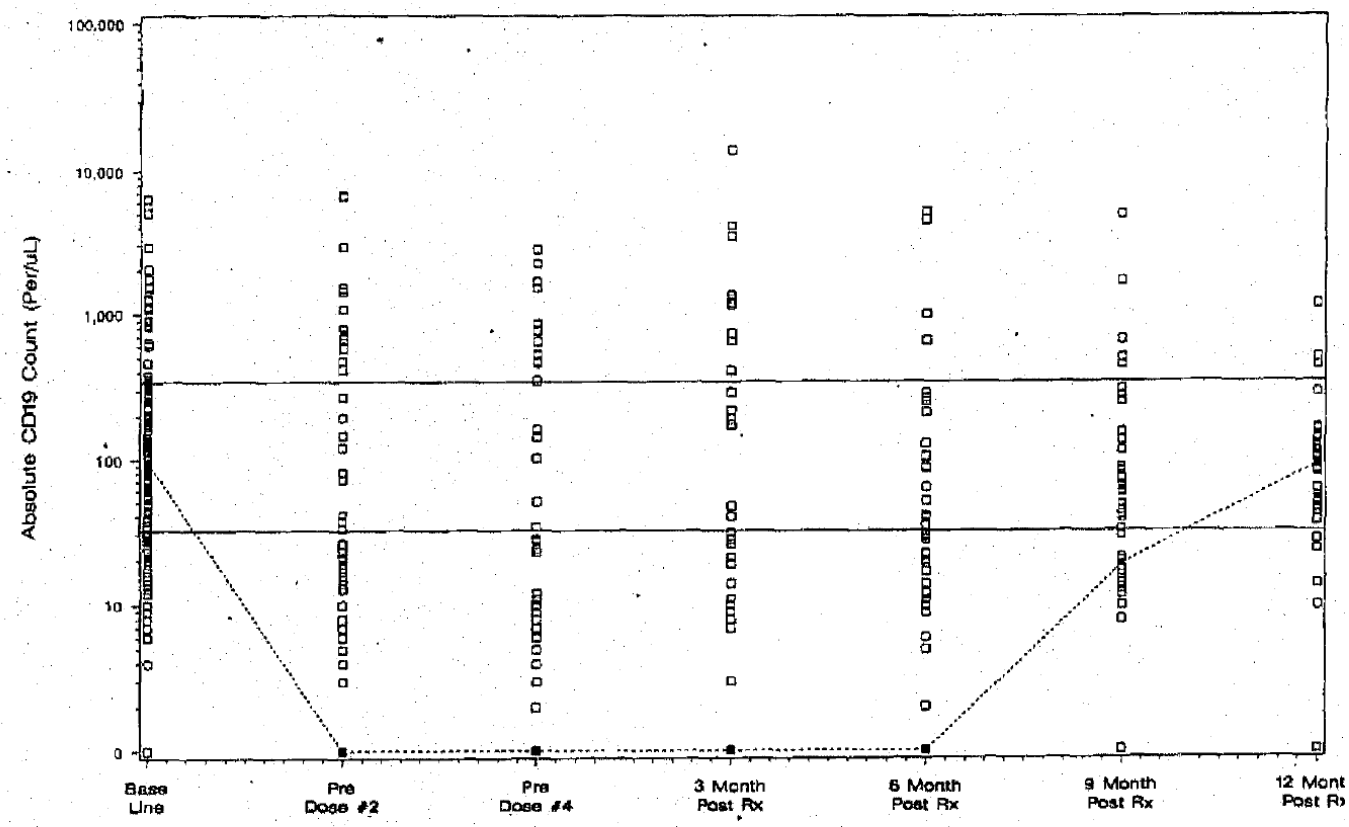


Fig 3. Median CD19+ lymphocyte counts (----) were depleted after 1 antibody infusion and recovered by 9 to 12 months. A minority of patients (n = 16) not deplete circulating B cells. These were predominantly SL patients (n = 13) and nonresponders (n = 15).

… … … … … … 2001

Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura

Roberto Stasi, Adalberto Pagano, Elisa Stipa, and Sergio Amadori

BLOOD, 15 AUGUST 2001 • VOLUME 98, NUMBER 4

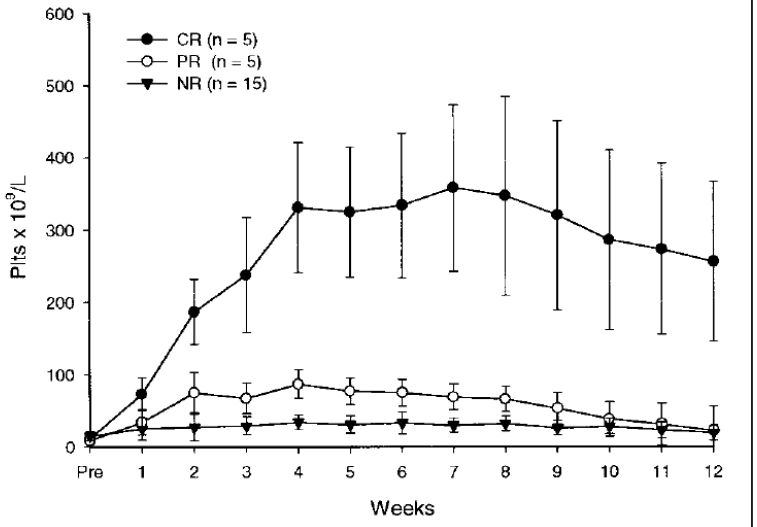


Figure 1. Platelet response to rituximab. Each data point represents the mean (± SD) platelet count at a particular time.

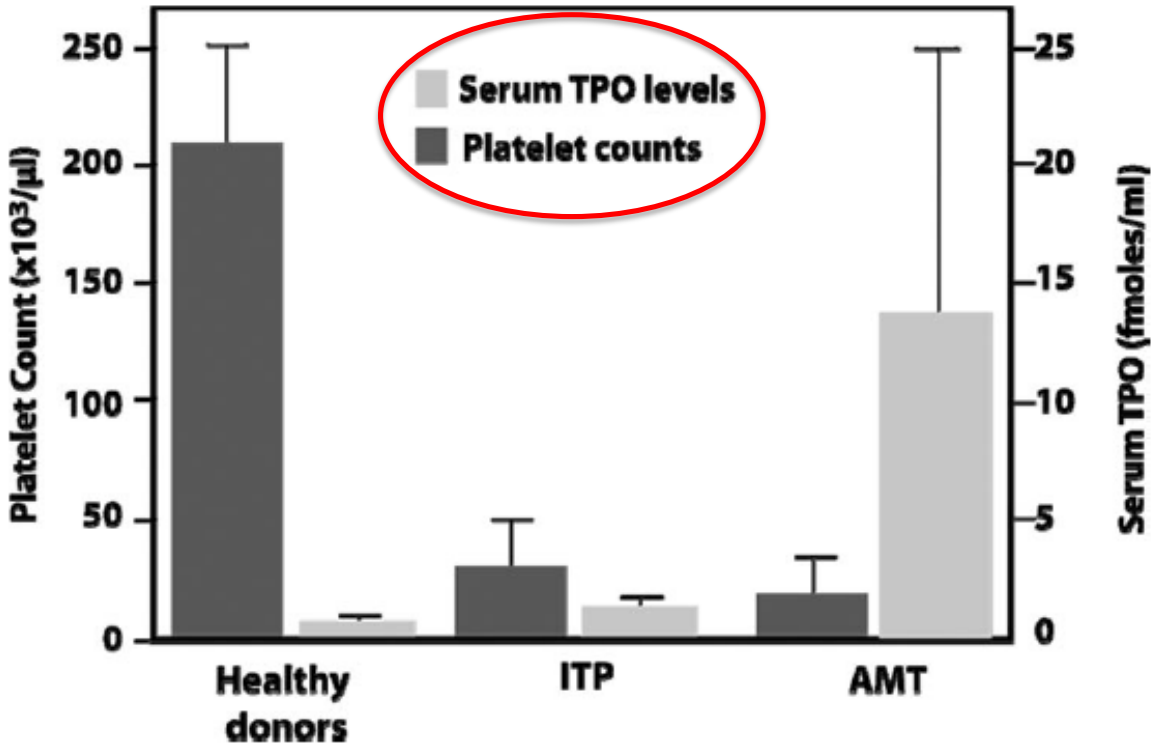
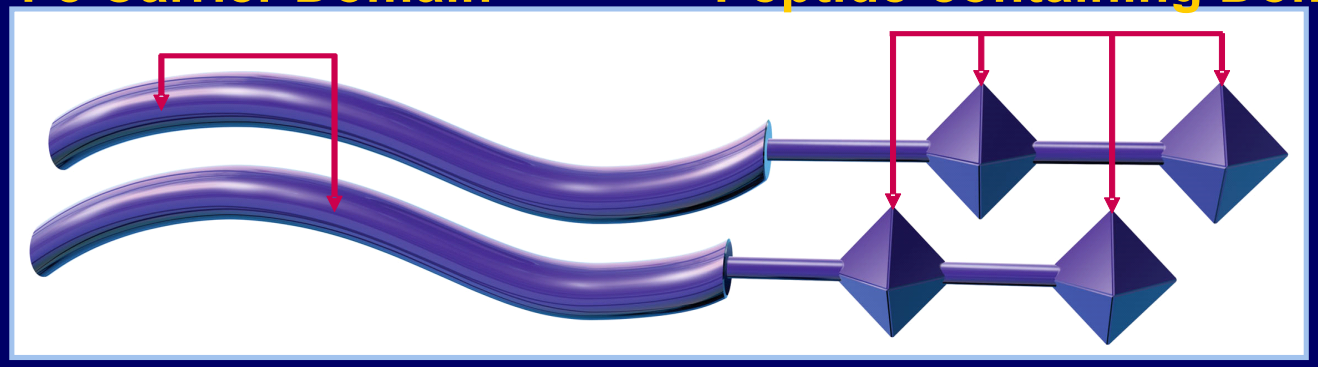


Figure 3. Serum TPO levels (light bars) and platelet counts (dark bars) are represented in healthy volunteers, patients with ITP, and patients with AMT. Compared with healthy volunteers, serum TPO levels are markedly elevated in AMT patients. TPO levels in ITP patients are only slightly higher despite similar lower platelet counts.

Gernsheimer T, the Oncologist 2009

Romiplostim: Structure

Fc Carrier Domain **Peptide-containing Domain**

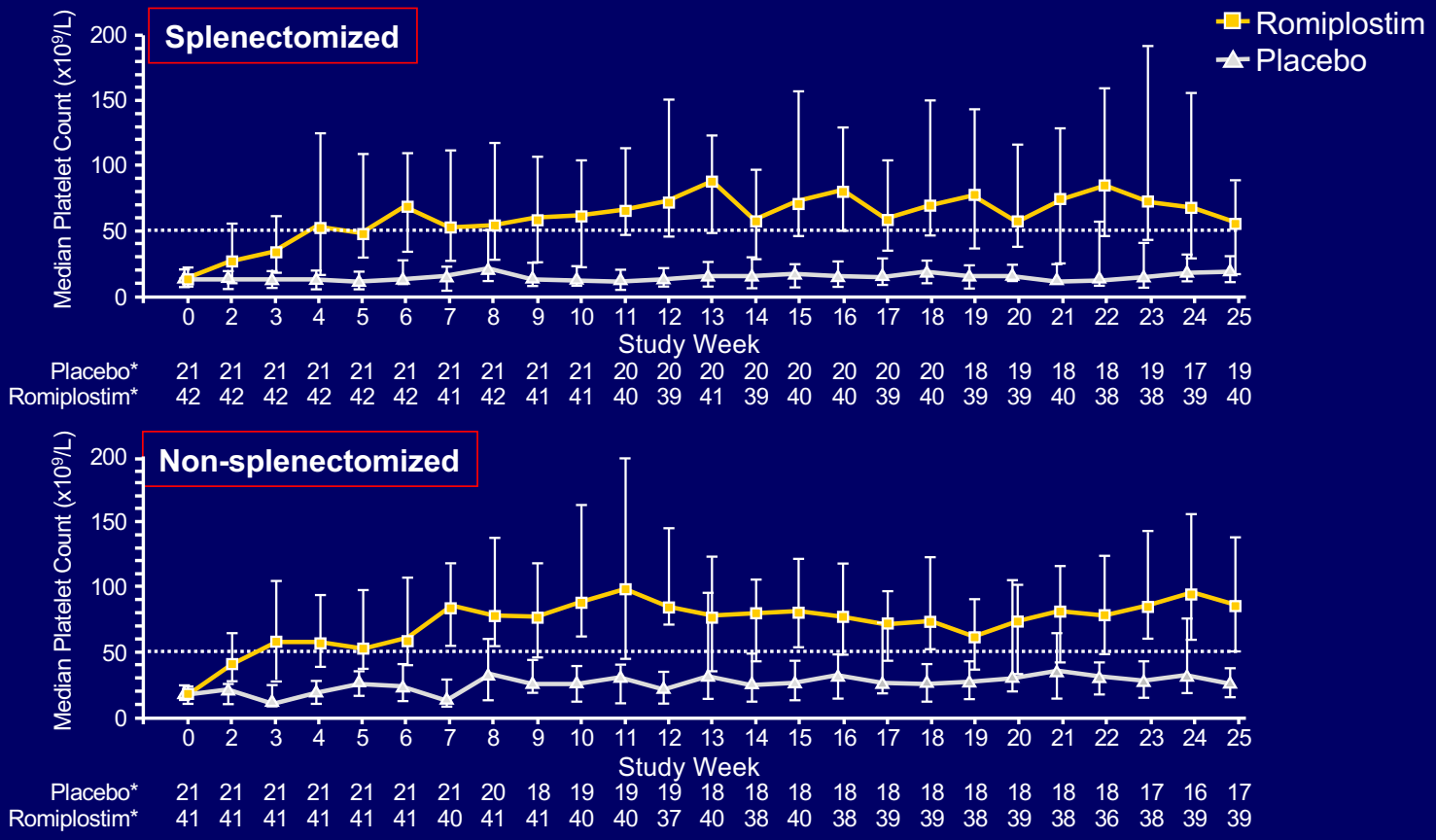


Romiplostim is a ‘peptibody‘ with two domains

- A peptide that binds TPOR characterizing the biological activity
  - There aren’t eTPO homologous sequences
- An antibody FC fraction, which increases the plasma half-life

Bussel et al. *N Engl J Med* 2006;355:1672–1681

Median Weekly Platelet Count

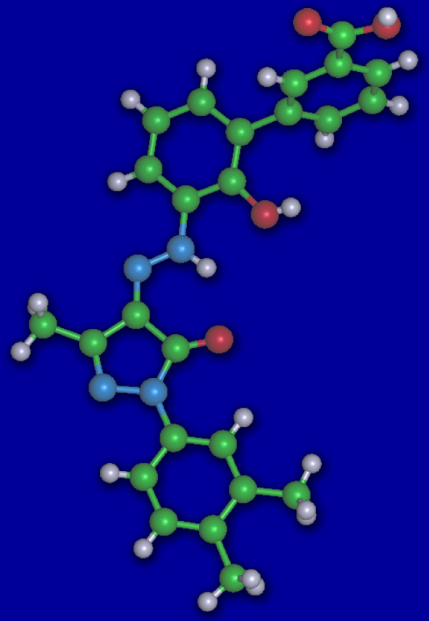


*Number available for measurement

Kuter et al. *Lancet* 2008;371:395–403

Eltrombopag

- Eltrombopag is a first-in-class[1], oral, non-peptide thrombopoietin (TPO) receptor (TPOR) agonist[2,3]
- Produces a dose-dependent increases in normally functioning platelets[4]
- Available as 25 and 50 mg film-coated tablets[5]



1. Erickson-Miller CL, et al. *Stem Cells* 2009; **27**: 424–30;
2. Bussel JB, et al. *N Engl J Med* 2007; **357**(22): 2237–47;
3. Stasi R, et al. *Drugs* 2008; **68**(7): 901–12;
4. Jenkins JM, et al. *Blood* 2007; **109**: 4739–41;
5. Garnock-Jones KP, et al. *Drugs* 2009; **69**(5): 567–76

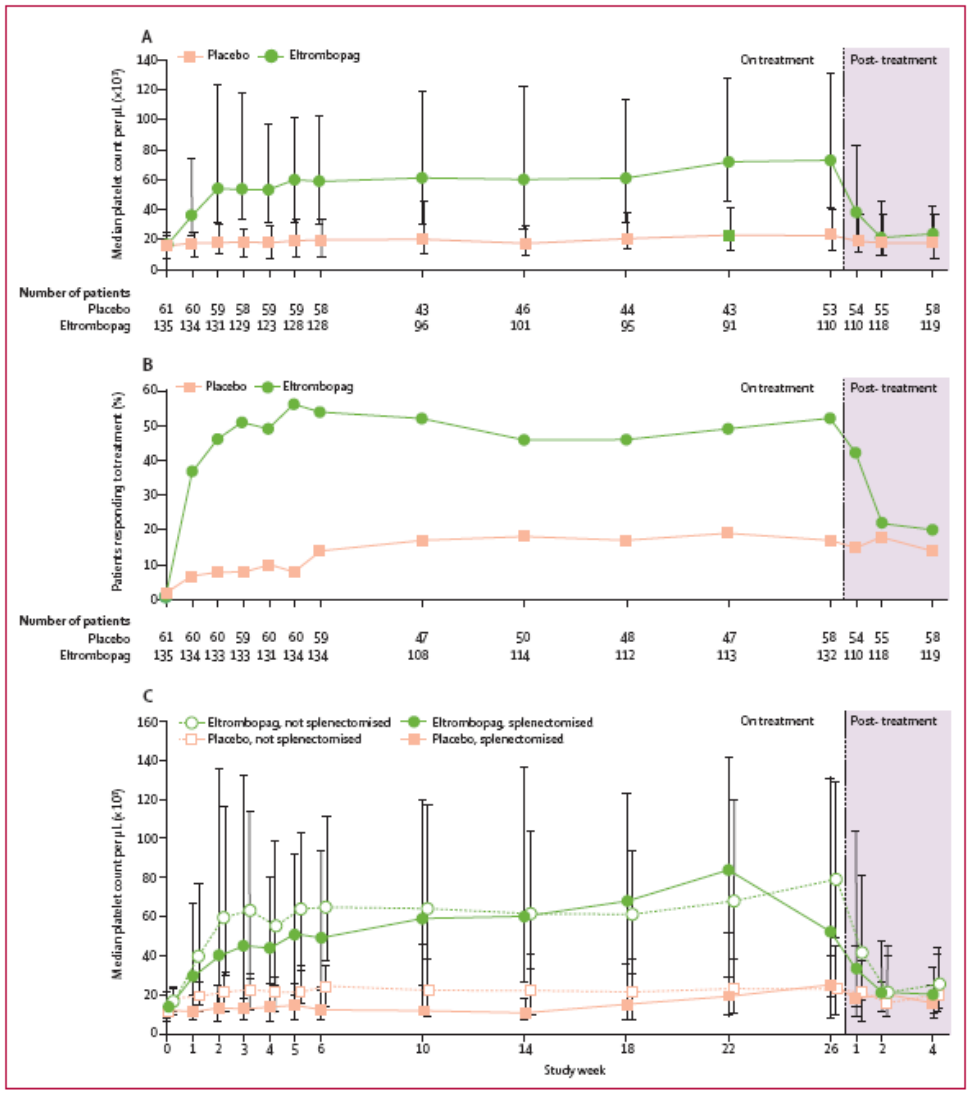


Figure 3: Median platelet counts (A), proportions of patients who responded to treatment (B), and median platelet counts by splenectomy status (C) at each nominal study visit
Patients responding to treatment were those who had a platelet count of 50 000–400 000 per µL at a study visit. Median platelet counts are shown with IQRs.

- **106/135 (79%) patients in the eltrombopag group responded to treatment at least once during study.**
- **Among these 64 (60%) responded at ≥75% of subsequent assessments**

- **Similar responses were reported irrespective of splenectomy status, baseline platelet count, or baseline treatment use**

Cheng G, et al. *Lancet* 2010

• 18/12/2009 Gazzetta Ufficiale: Nplate erogabile in fascia H, nei pz. Con ITP cronica splenectomizzati refrattari ad altri trattamenti (ad es. Corticosteroidi e immunoglobuline) o in II linea quando la splenectomia è controindicata

• 22/02/2011 Gazzetta Ufficiale: Revolade erogabile in fascia H, nei pz. Con ITP cronica splenectomizzati refrattari ad altri trattamenti (ad es. Corticosteroidi e immunoglobuline) o in II linea quando la splenectomia è controindicata

- **11/09/2017 Gazzetta Ufficiale n°212: Nplate erogabile in fascia H, nei «pz. adulti affetti da porpora trombocitopenica autoimmune (idiopatica) cronica (ITP) , che sono refrattari ad altri trattamenti (ad esempio corticosteroidi, immunoglobuline)»**

- **17/8/2020 Gazzetta Ufficiale n°204: Revolade erogabile in fascia H, «è indicato in pazienti di età superiore ad un anno per il trattamento della trombocitopenia immune primaria (ITP) della durata di almeno sei mesi dalla diagnosi e che sono refrattari ad altri trattamenti (ad esempio corticosteroidi, immunoglobuline)»**

Emerging drugs for immune thrombocytopenia (ITP)

Abdulgabar Salama **Expert opinion on emerging drugs, 2017**

Table 2. Competitive environment table for drugs under investigation for ITP.

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
PRTX-100	Protalex	A highly purified form of SpA **(Staph protein A)**	ITP	Phase II	Immunosuppressant
Alemtuzumab	Millenium und Genzyme/Bayer	A humanized McAb that targets CD52	None	Phase II trial in patients with autoimmune cytopenias, including ITP	CD52 antagonist; lymphocyte inhibitor
CTLA4-Ig (RG-2077; RG-1059)	RepliGen	A fully human recombinant fusion protein	None	Refractory ITP: Phase I/II trial in UK	CD80/CD86 antagonist; T-cell inhibitor
CTLA4-Ig (Abatacept; BMS-188667)	Bristol-Myers Squibb (BMS)	A fully human recombinant fusion protein	None	Launched for RA	CD80/CD86 antagonist; T-cell inhibitor
Belimumab (Lymphostat-B®)	Human Genome Sciences (HGS) & GlaxoSmithKline (GSK)	A human McAb against BAFF/BLyS	None	Phase III trial in systemic lupus erythematosus (SLE); phase II trial in RA	BAFF/BLyS antagonist; inhibiting B-cell survival
TACI-Ig (Atacicept)	ZymoGenetics & Merck Serono	A soluble decoy IgG fusion protein of TACI	None	Phase III trial in SLE; phase II trial in RA and MS	Antagonist for BAFF/BlyS and APRIL; inhibiting B-cell survival
BR3-Fc	Biogen Idec & Genentech	A soluble decoy IgG fusion protein of BR3	None	Phase II trial in RA	BAFF/BLyS antagonist; inhibiting B-cell survival
AMG 623	Amgen & Anthera	Consisting of Fc conjugated to a peptide	None	Phase I trial in SLE	BAFF/BLyS antagonist; inhibiting B-cell survival
Blisibimod	Anthera Pharmaceuticals	Fusion protein	Nonrenal SLE	Phase III study in progress	Inhibiting BAFF on B cells
Tabalumab	Eli Lily	Monoclonal antibody	Nonrenal SLE	Phase III study in progress	Blocking both soluble and membrane-bound BAFF on B cells

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Abdulgabar Salama **Expert opinion on emerging drugs, 2017**

Table 2. Competitive environment table for drugs under investigation for ITP.

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Rituximab	Roche	Monoclonal antibody	Nonrenal and renal SLE	Phase III studies	Depleting B cells
Epratuzumab	UCB and Immunomedics	Monoclonal antibody	Nonrenal SLE	Phase III studies in progress	Modulating B-cell signaling, cellular activation and survival
Abatacept	BMS	Fusion protein	Nonrenal and renal SLE	Phase III studies	Blocking co-stimulatory signals between T and B cells
Rigerimod	ImmuPharma	Peptide	Nonrenal SLE	Phase II studies	Tolerizing T cells
Laquinimod	Teva	Small molecule	Renal SLE	Phase IIa study	Modulating T-cell actions
Tocilizumab	Roche	Monoclonal antibody	Nonrenal SLE	Phase I study	Blocking IL-6 receptor
Sirukumab	Centocor	Monoclonal antibody	Cutaneous lupus	Phase I study	Blocking IL-6
Sifalimumab	MedImmune	Monoclonal antibody	Nonrenal SLE	Phase I study	Blocking type I interferon
Rontalizumab	Genentech	Monoclonal antibody	Nonrenal SLE	Phase II study	Blocking type I interferon
Eculizumab	Alexion Pharmaceuticals	Monoclonal antibody	Nonrenal SLE	Phase I study	Blocking complement C5
BMS-986004	Bristol-Myers-Squibb	Anti-CD40 L Fc-fusion protein	ITP	Phase I/II trial	Binds to CD40L expressed on T lymphocytes, prevents T-cell-mediated proliferation and differentiation of B cells
UCB7665	UCB Biopharma S.P.R.L.	Humanized IgG4	ITP	Phase II	Immunosuppressant

….avatrombopag, lusutrombopag, rozanolixizumab, fostamatinib….

Grazie per l’attenzione…..

Thrombotic thrombocytopenic purpura (TTP)

Rare and life-theatening **thrombotic microangiopathy** characterized by small blood vessels platelets-rich thrombi resulting in a low platelet count, microangiopathic hemolytic anemia and ischemic organ damage.

- Prevalence: 10 cases/million people/year
- Incidence: 1 new case/million people/year
- 2-fold more frequent in woman
- Relapsing tendency
- Rapid recognition is crucial

1924 Dr. Eli Moschcowitz

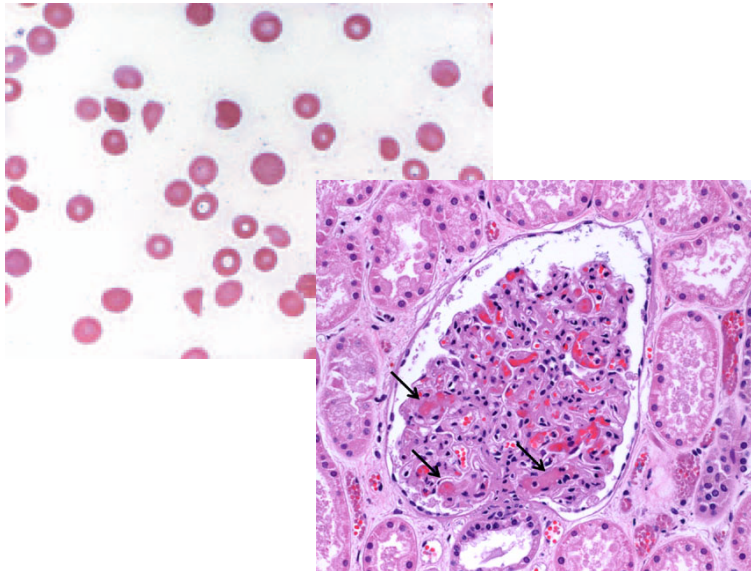
Described a 16-years girl with fever, anemia and weakness who subsequently developed paralysis and coma in the 2 weeks leading to her death.

Authopsy revealed disseminated hyaline thrombi in the small arterioles and capillaires of the heart, kidney and liver, but the moderate-size vessels were unaffected.

1966 Dr. Amorosi & Ultman

«Classic pentad»:

- Microangiopathic hemolytic anemia
- Thrombocytopenic purpura
- Fever
- Neurologic abnormalities
- Renal disease



Idiopathic TTP

- **severe thrombocytopenia** (typically <30 × 10^9/L)
- **microangiopathic hemolytic anemia (MAHA)**
- corresponding symptoms (ie, skin and mucosal hemorrhage, weakness, and dyspnea).

Symptoms related to organ ischemia/infarction:

- ~60% of patients: **neurologic symptoms** (from headache and confusion to stroke, coma, and seizures).
- ~25% of patients: **heart ischemia** (from isolated electrocardiographic abnormalities to myocardial infarction)
- ~35% of patients: **mesenteric ischemia** (abdominal pain)
- **Renal manifestations** mainly of an isolated proteinuria/hematuria; typically a serum creatinine level < 2 mg/dL; acute renal failure is unusual.

ADAMTS13 activity < 10%

1982 Dr. Moake

«unusually large» multimers of von Willebrand factor (vWF) in plasma of patients with relapsing TTP

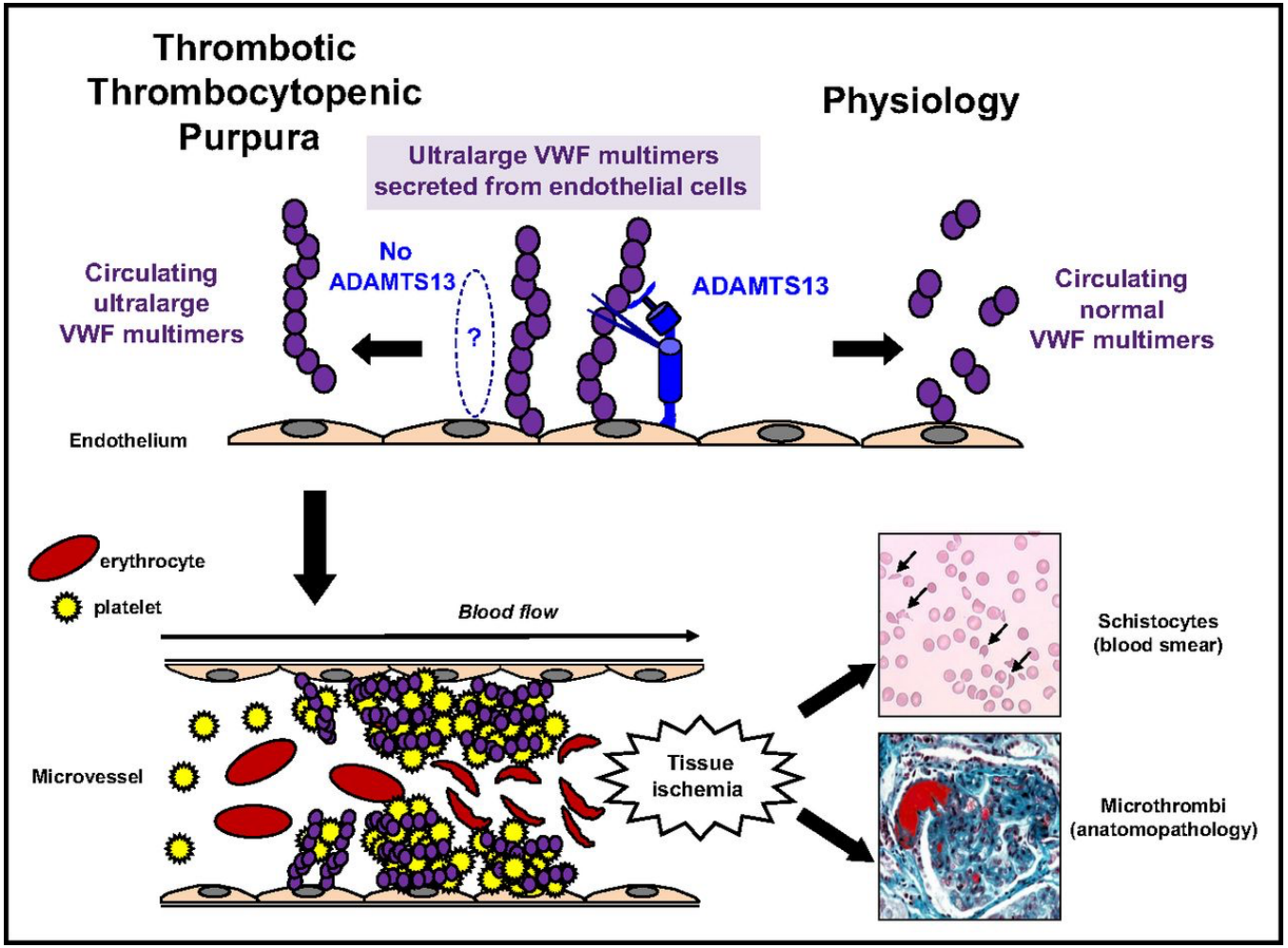
1997 Dr. Furlan – 1998 Dr. Tsai

Deficient activity of vWF cleaving protease in patients with hereditary and acquired relapsing TTP

2001: Zheng – Gerritsen – Fujikawa – Levy - Soejima

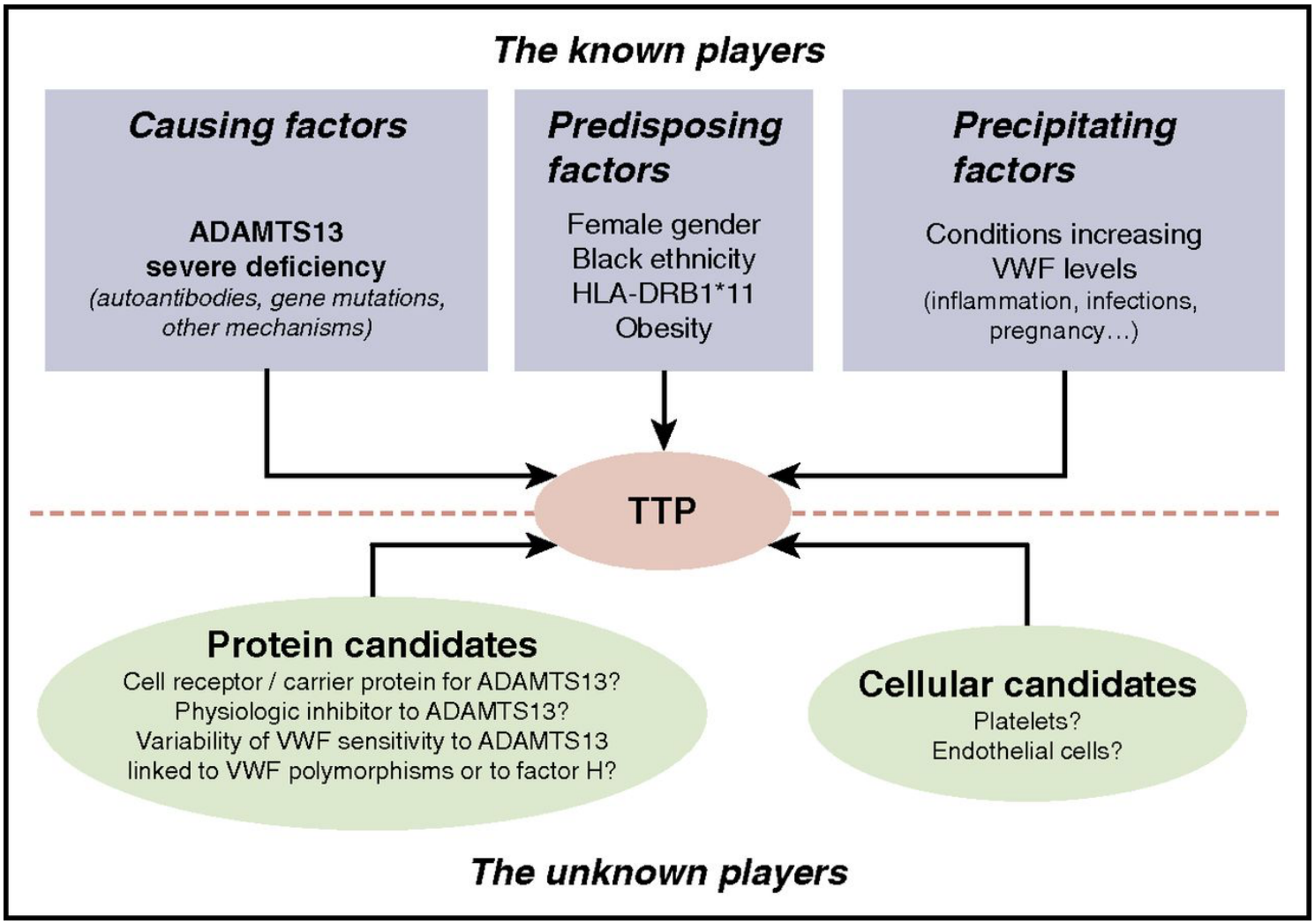
Purified the specific vWF cleaving **protease ADAMTS13**

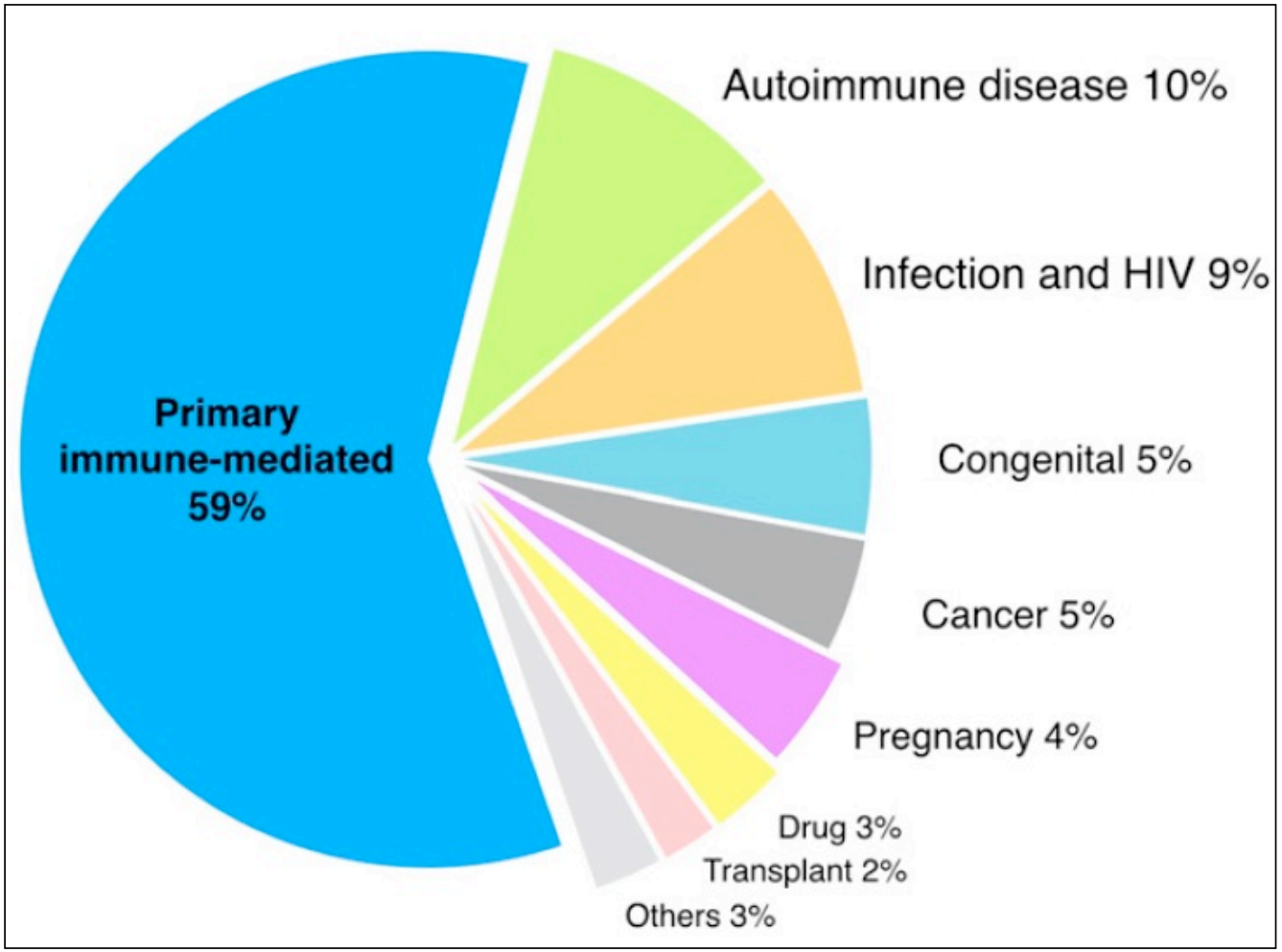
(A Disintegrin and Metalloprotease with ThromboSpondin type 1 motif, member 13)



- **ACQUIRED** (95%)
  ADAMTS13 deficiency due to IgG autoantibodies

- **INHERITED** (5%)
  mutations of the ADAMTS13 gene





Chiasakul T and Cuker A, Blood 2019

Clinical-laboratoristic predictor factors

Table 3. Comparison of clinical prediction scores for severe ADAMTS13 deficiency

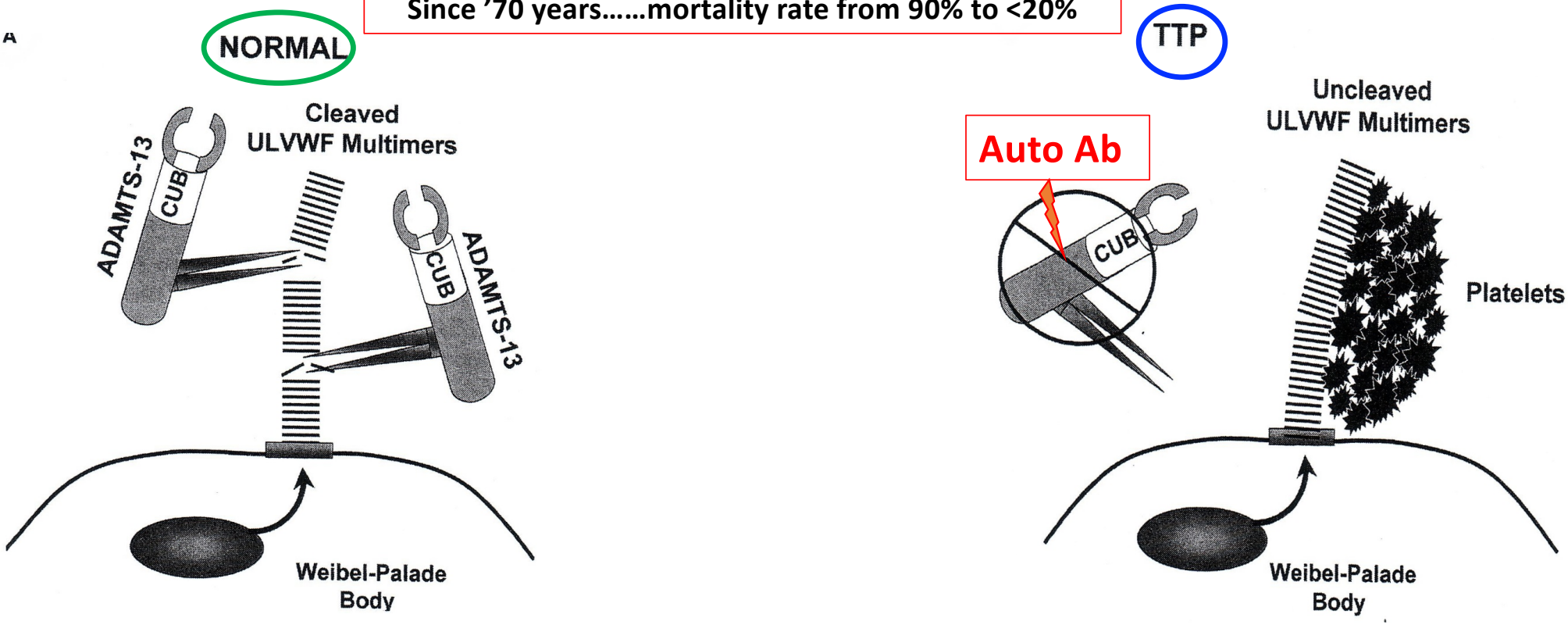
	PLASMIC score	French score, points	Bentley score, points
Component of score			
Platelet count	$<30 \times 10^9$/L: 1 point	$\leq 30 \times 10^9$/L: 1 point	$>35 \times 10^9$/L: −30 points
Creatinine level	<2 mg/dL: 1 point	≤2.26 mg/dL: 1 point	>2 mg/dL: −11.5 points
Parameters of hemolysis	Reticulocyte count >2.5%: 1 point Haptoglobin undetectable: 1 point Indirect bilirubin >2 mg/dL: 1 point	—	Reticulocyte: >3% +21 points Indirect bilirubin >1.5 mg/dL: +20.5 points
Associated conditions	No active cancer: 1 point No history of solid-organ or hematopoietic stem cell transplant: 1 point	—	—
MCV	<90 fL: 1 point	—	—
INR	<1.5: 1 point	—	—
ANA	—	Positive: 1 point	—
D-dimer	—	—	>4 mcg/mL: −10 points
Interpretation			
Risk category, total score			
Low	0-4	0	<20
Intermediate	5	1	20-30
High	6-7	2-3	>30

Chiasakul T and Cuker A, Blood 2019

Treatment is guided by pathophysiology

Plasma-exchange and HD steroids

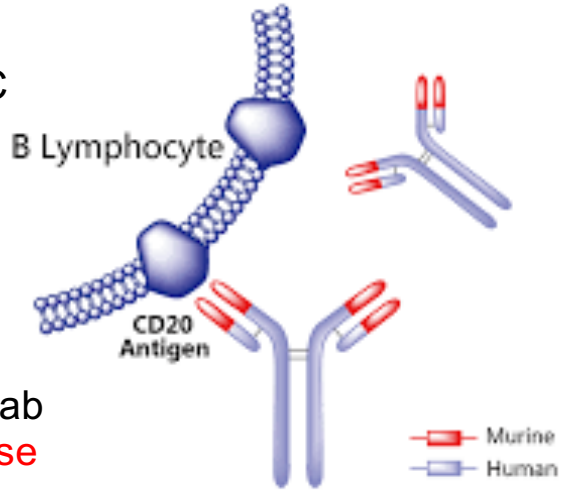
Since ’70 years……mortality rate from 90% to <20%



Suppressing anti-ADAMTS13 antibodies

Rituximab

Is remarkably effective at killing the ADAMTS13-specific B cells that mature in PC and stopping autoantibody production.

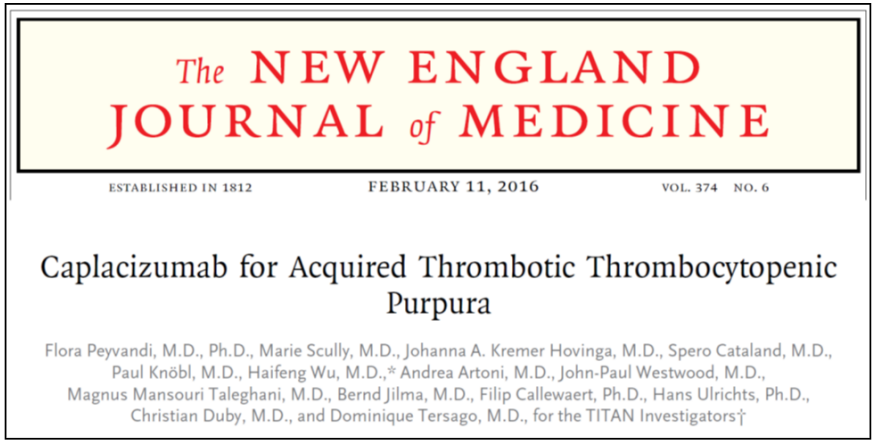


- First introduced in patients with a suboptimal response to conventional treatment **(Chemnitz J et al. AJH 2002)**.

- In 4 **retrospective studies**, 57 patients with TTP were treated with rituximab (in most instances, 375 mg/m^2 in 4 weekly doses) after suboptimal response to standard treatment. Remission was achieved in 51/57 (89%) cases, typically in less than 4 weeks.
- In 2 **prospective studies**, involving 47 patients with a refractory or recurrent disease, rituximab 375 mg/m^2 administrated within 2 to 3 weeks resulted in remission in 98% of cases within the first month of diagnosis. No relapse was observed during the first year of follow-up, but there were relapses beyond 1 year.

Inhibiting vWF-platelet interactions

- Is a bivalent (nanobody) humanized llama immunoglobulin variable region that recognizes the human vWF A1 domain and prevents binding to platelet GPIb.



The NEW ENGLAND JOURNAL of MEDICINE

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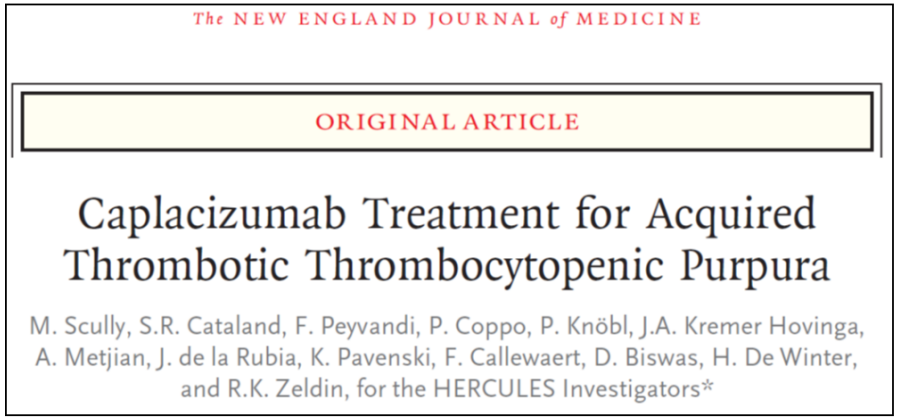
Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

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†

A phase 2, controlled study (75 pts):
The primary end point was the time to a response, defined as confirmed normalization of the platelet count.
Major secondary end points included exacerbations and relapses.

Caplacizumab induced a faster resolution of the acute TTP episode than did placebo. The platelet-protective effect of caplacizumab was maintained during the treatment period.
Caplacizumab was associated with an increased tendency toward bleeding, as compared with placebo.



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*

A Phase III Double-Blind, Randomized, Parallel Group, Multicenter Placebo-Controlled Trial (145 pts):
The primary outcome was the time to normalization of the platelet count, with discontinuation of daily plasma exchange within 5 days thereafter.
Secondary outcomes included a composite of TTP-related death, recurrence of TTP, or a thromboembolic
event during the trial treatment period

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.

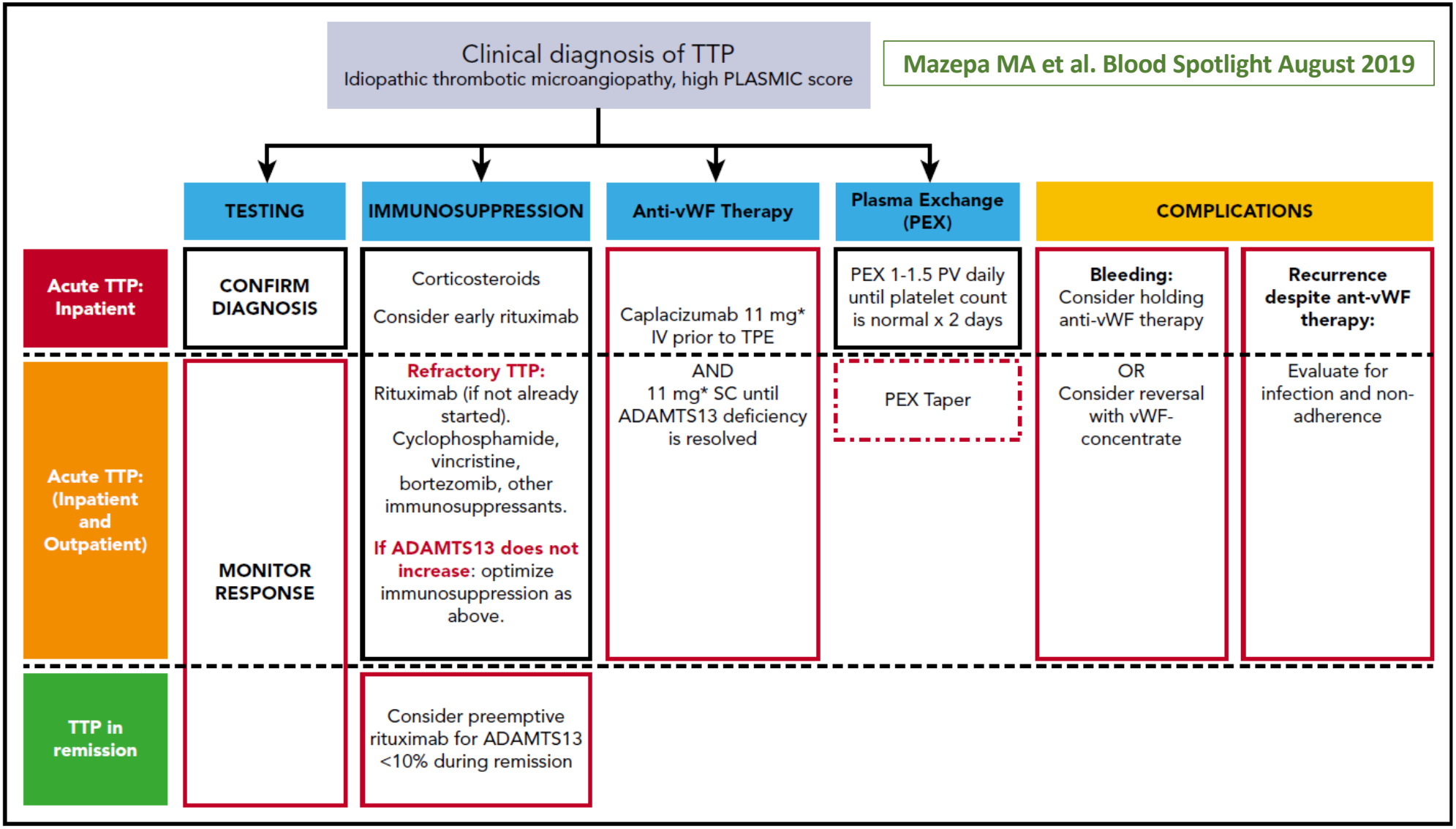
Definitions

Exacerbations: defined as recurrent thrombocytopenia within 30 days after the end of daily PE, that required the reinitiation of daily PE.

Relapse: defined as a TTP event occurring more than 30 days after the end of daily PE

Complete remission: confirmed normalization of platelet count and absence of exacerbation after initial daily PE course

Peyvandi F. et al. NEJM 2016


Clinical diagnosis of TTP
Idiopathic thrombotic microangiopathy, high PLASMIC score
Mazepa MA et al. Blood Spotlight August 2019
TESTING
IMMUNOSUPPRESSION
Anti-vWF Therapy
Plasma Exchange (PEX)
COMPLICATIONS
Acute TTP: Inpatient
CONFIRM DIAGNOSIS
Corticosteroids
Consider early rituximab
Caplacizumab 11 mg* IV prior to TPE
PEX 1-1.5 PV daily until platelet count is normal x 2 days
Bleeding: Consider holding anti-vWF therapy
Recurrence despite ant-vWF therapy:
Acute TTP: (Inpatient and Outpatient)
MONITOR RESPONSE
Refractory TTP: Rituximab (if not already started). Cyclophosphamide, vincristine, bortezomib, other immunosuppressants.
If ADAMTS13 does not increase: optimize immunosuppression as above.
AND
11 mg* SC until ADAMTS13 deficiency is resolved
PEX Taper
OR
Consider reversal with vWF-concentrate
Evaluate for infection and non-adherence
TTP in remission
Consider preemptive rituximab for ADAMTS13 <10% during remission

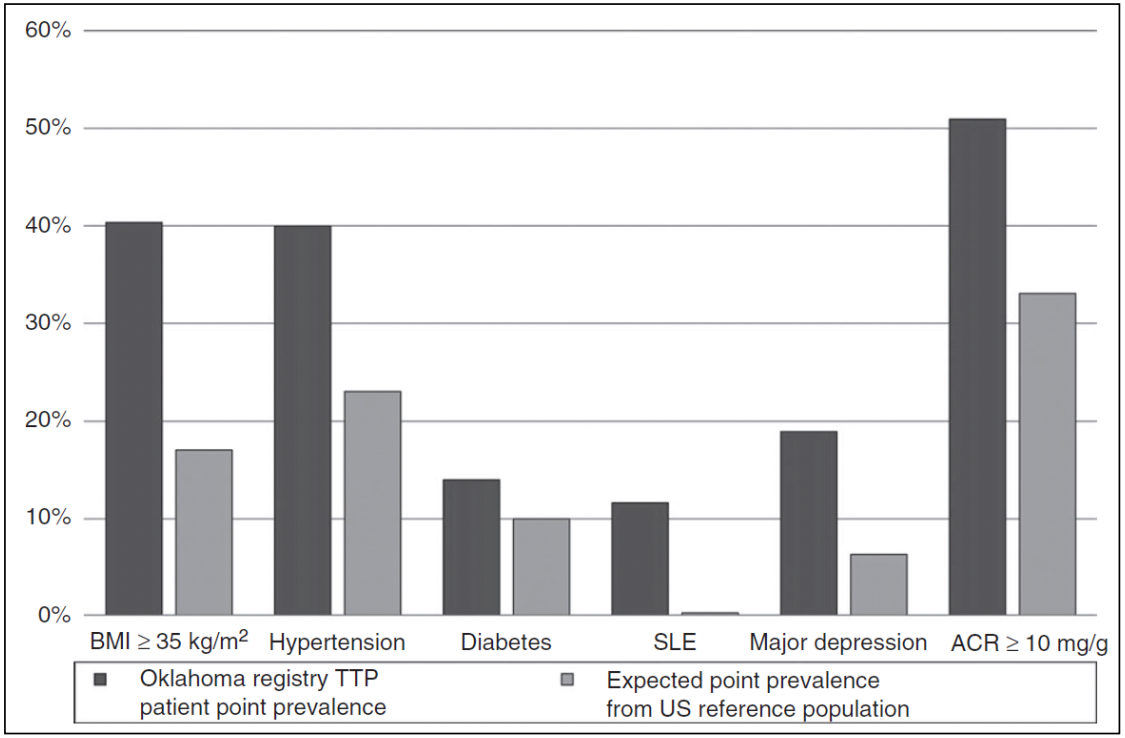
Long-term follow-up in survivors of TTP

Life after acquired thrombotic thrombocytopenic purpura: morbidity, mortality, and risks during pregnancy

S. K. VESELY
Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Vesely SK, J Thromb Haemost 2015

- TTP survivors are a vulnerable population with higher than expected rates of chronic morbidities:
  - Hypertension (40% vs 30%)
  - Depression requiring treatment (19% vs 6%)
  - Chronic kidney disease
  - Sistemic Lupus Erythemathosus
  - Obesity
  - Cognitive impairment
  - Overall poor quality of life



iTTP main highlights

- **Differential diagnosis**
- **Treatments: PE ± steroids, Rituximab, Caplacizumab…..others?...**
- **Mortality < 20%**
- **Relapse 30-50%, most common during the first two years after initial diagnosis**
- **ADAMTS13 activity during TTP remission phase is emerging as a predictor of relapse….**
- **What is the best to prevent relapse?.....Rituximab?**
- **What is the fate of those who survive the TTP?**