Gestione dei pazienti con ITP

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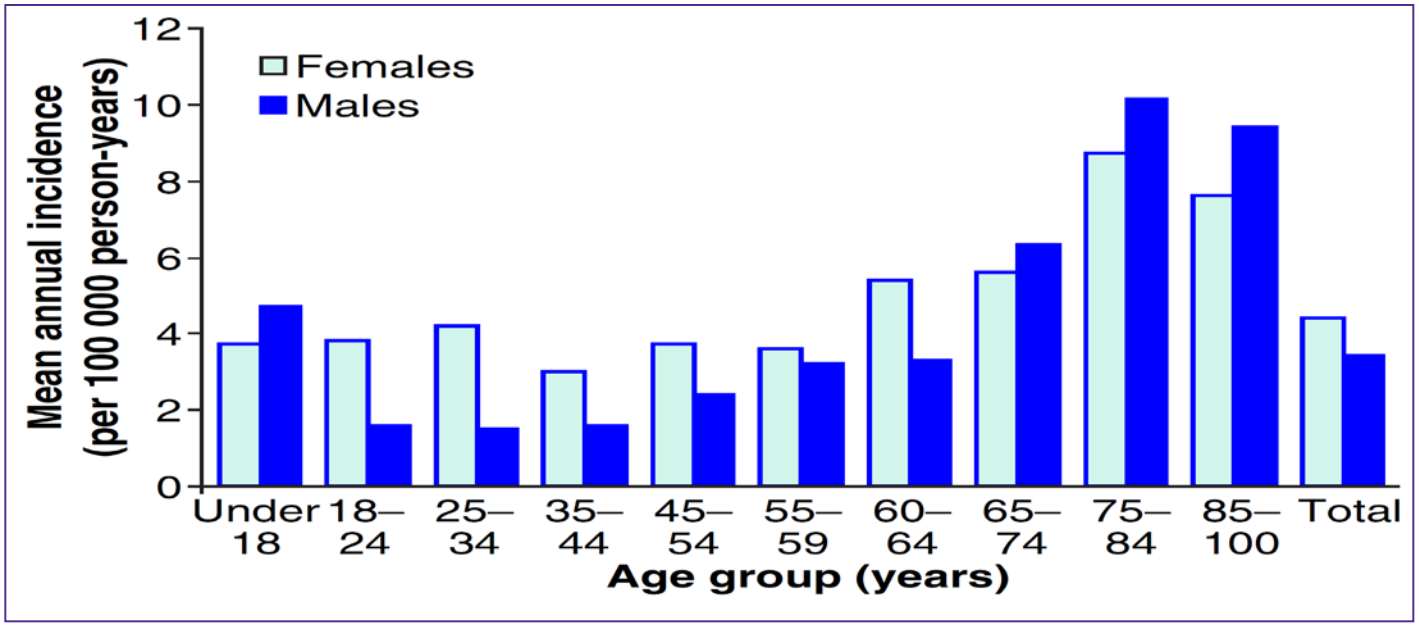
SISET
SOCIETA' ITALIANA PER LO STUDIO DELL'EMOSTASI E DELLA TROMBOSI

Incidenza della PTI

- In Europa, il numero stimato di pazienti adulti/anno con nuova diagnosi di PTI va da **1 a 4 per 100.000** persone[1]
- **L'incidenza tende ad aumentare con l'età**; con l'aumentata aspettativa di vita, anche il numero di pazienti con PTI e conseguenti comorbidità è destinato ad aumentare[1]
- In uno studio danese, il tasso di incidenza è più che raddoppiato nei pazienti di età > 60 anni rispetto ai pazienti più giovani; i risultati sono stati confermati da uno studio di coorte condotto in UK, con la più alta incidenza di PTI osservata nei pazienti > 60 anni[1]



Studio UK - Distribuzione della PTI per fasce d'età: 1990-2005[2]

1. Michel M. *Eur J Haematol* 2009; 82 (suppl. 71): 3-7

2. Schoonen et al. *Br J Haematol* 2009;145; 235-244

- La mortalità complessiva è inferiore all'1-2%
- Non è chiaro se la gravità dei sintomi abbia significato prognostico in relazione al rischio di sanguinamenti pericolosi per la vita
- In una recente meta-analisi condotta su 29 studi il tasso pesato di emorragie intracraniche risultava dello 0,5% nei bambini e dell'1,5% negli adulti, con maggior frequenza nelle fasi croniche. Per quanto riguarda i sanguinamenti gravi non intracranici il tasso di emorragie era più frequente nei bambini (20,2%) che negli adulti (9,6%) (Neunert C, et al 2015).
- una grave piastrinopenia (< 10-20 x 10^9/L), precedenti manifestazioni emorragiche ed età avanzata sembrano indicare un aumentato rischio di emorragie maggiori (Arnold DM, 2015)

blood 2009 113: 2386-2393
doi:10.1182/blood-2008-07-162503 originally published online November 12, 2008

Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group

Francesco Rodeghiero, Roberto Stasi, Terry Gernsheimer, Marc Michel, Drew Provan, Donald M. Arnold, James B. Bussel, Douglas B. Cines, Beng H. Chong, Nichola Cooper, Bertrand Godeau, Klaus Lechner, Maria Gabriella Mazzucconi, Robert McMillan, Miguel A. Sanz, Paul Imbach, Victor Blanchette, Thomas Kühne, Marco Ruggeri and James N. George

Recommendations

Definition of primary and secondary immune thrombocytopenia (primary and secondary ITP) and platelet count threshold

The panel decided to avoid the term "idiopathic," preferring "immune," to emphasize the immune-mediated mechanism of the disease and to choose "primary" (as opposed to idiopathic) to indicate the absence of any obvious initiating and/or underlying cause. The term "purpura" was felt inappropriate, because bleeding symptoms are absent or minimal in a large proportion of cases.[17,18]

Immune **T**hrombocyto**P**enia: **ITP**

Immune ThrombocytoPenia: ITP

- ITP — YES — already used in scientific literature
- ~~Idiopathic~~ — No — evidence of autoimmune mechanisms
- ~~Purpura~~ — No — no hemorragic manifestations in many cases

blood
2009 113: 2386-2393
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Immune ThrombocytoPenia: ITP

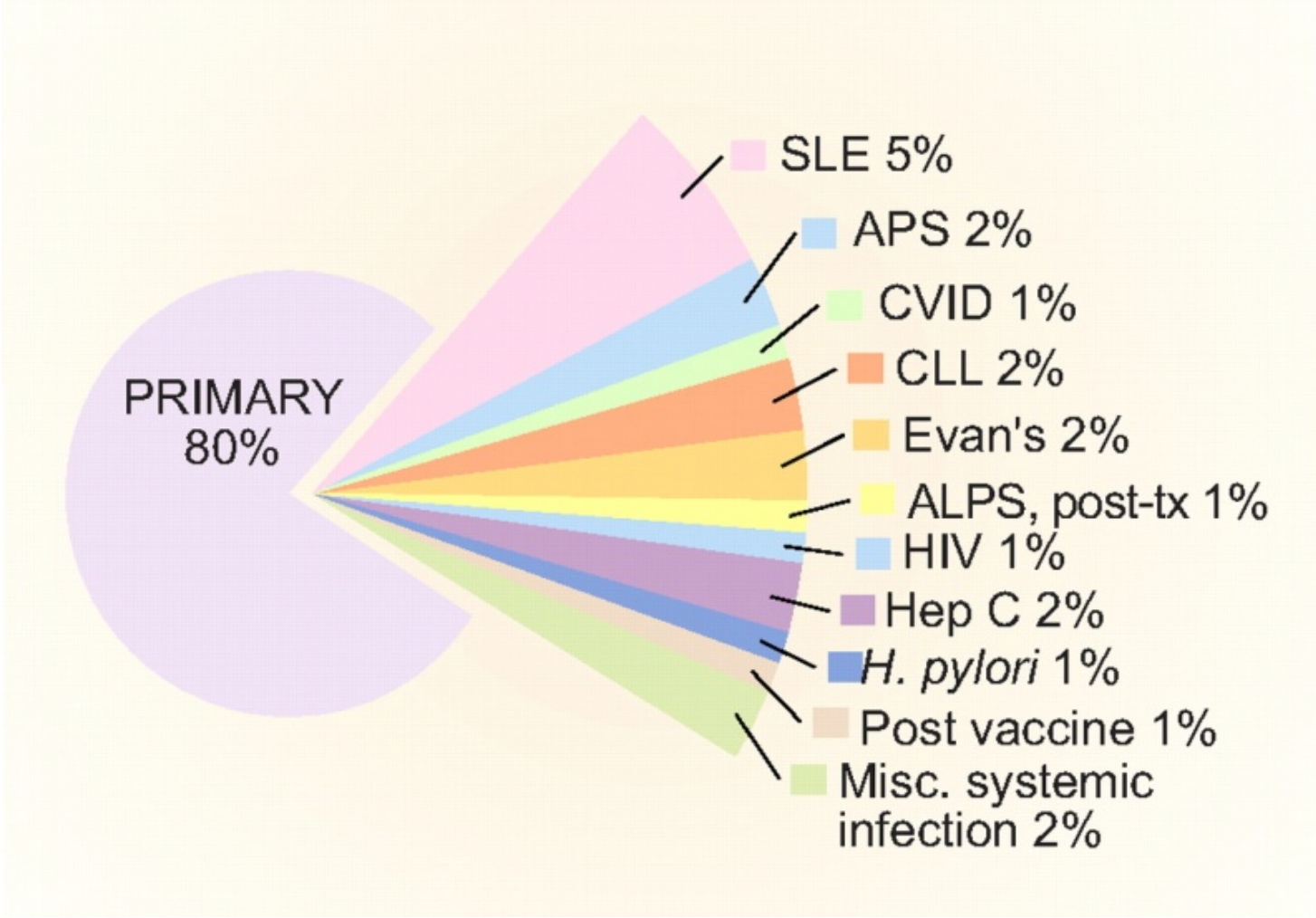
- **Primary**
  - Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count **100 x10^9/L**) in the absence of other causes or disorders that may be associated with thrombocytopenia.
  - The diagnosis of primary ITP remains one of exclusion;
- **Secondary**
  - All forms of immune-mediated thrombocytopenia except primary ITP
  - The acronym ITP should be followed by the name of the associated disease for example, **"secondary ITP (lupus-associated),"** **"secondary ITP (HIV-associated),"** and **"secondary ITP (drug-induced)."**
  - For manuscript titles, abstracts, and so on, definitions such as **lupus-associated ITP** or HIV-associated ITP can also be used.
- **????**
  - Positive Lupus anticoagulant test
  - Antinuclear antibodies (without clinical manifestations)
  - Anticardiolipin antibodies (without clinical manifestations)

blood

Prepublished online Apr 24, 2009;
doi:10.1182/blood-2009-01-129155

The ITP syndrome: pathogenic and clinical diversity

Douglas B. Cines, James B. Bussel, Howard A. Liebman and Eline T. Luning Prak



Immune ThrombocytoPenia: ITP

PLoS Medicine | www.plosmedicine.org 0388 March 2006 | Volume 3 | Issue 3 | e24

OPEN ACCESS Freely available online PLOS MEDICINE

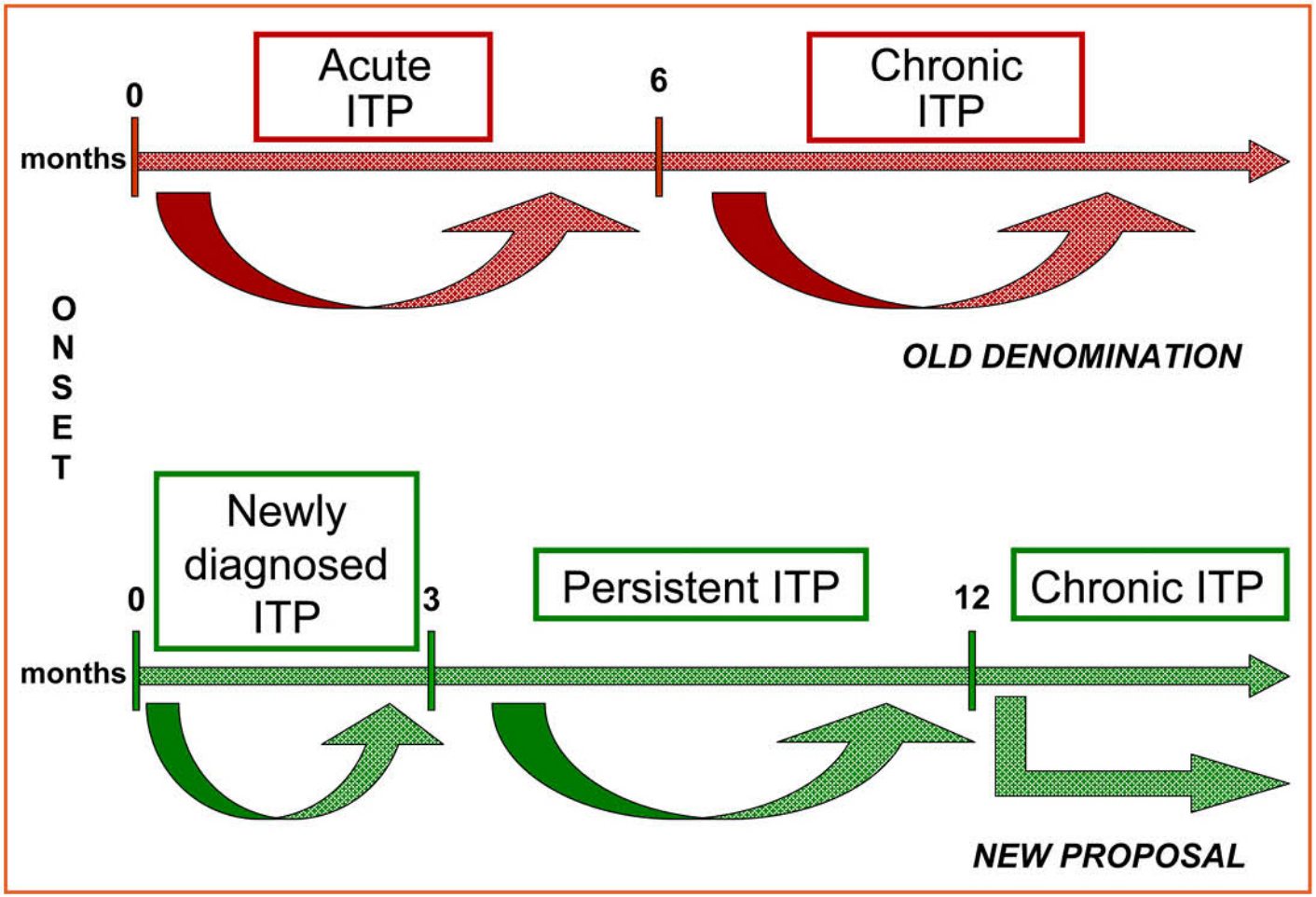
Long-Term Outcome of Otherwise Healthy Individuals with Incidentally Discovered Borderline Thrombocytopenia

Roberto Stasi[1*], Sergio Amadori[2], John Osborn[3], Adrian C. Newland[4], Drew Provan[4]

- Why $100x10^9/L$ if lower value in normal range is considered 120-150 $x10^9/L$?

"This is to avoid inappropriate diagnostic assessment in a large number of cases"

- 191 people who had borderline thrombocytopenia. In 64% of those people, the platelet count became normal or stayed low with no other illness.
- **Over 10 years, there was a 6.9% chance of thrombocytopenia and a 12% chance of another autoimmune disorder occurring.**


Acute ITP
Chronic ITP
0
6
months
ONSET
OLD DENOMINATION
Newly diagnosed ITP
Persistent ITP
Chronic ITP
0
3
12
months
NEW PROPOSAL

Immune Thrombocytopenia: ITP

Disease Severity (before)

- Mild
- Moderate
- Severe

Severe ITP (now)

Presence of bleeding symptoms at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose

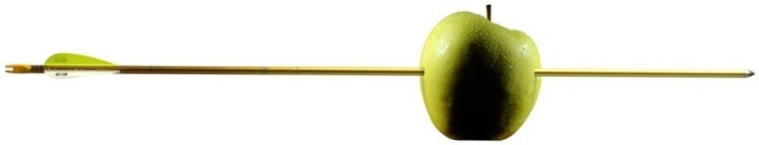
Platelets Count

Clinical Manifestations

Description of bleeding symptoms and signs of hemorrhages.

(is a very complex topic which requires a lot of time …. we fortunately don't have!)

- None of the few bleeding assessment tools available in the literature could be easily adopted and/or were validated for ITP.
- Terms such as "mild" or "moderate" ITP were discouraged because their vagueness.
- The IWG concluded that a new system based on the consensus of clinicians who are experts in adult and pediatric ITP should be proposed



To have a <u>single tool for both children and adults</u>

- to standardize description of the hemorrhages at presentation and during the different phases,
- to assess the overall impact of treatments,
- to correlate with QoL, platelet count, age, gender, etc.
- to be used in research studies.

blood®
2013 121: 2596-2606
doi:10.1182/blood-2012-07-442392 originally published online January 29, 2013

Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group

Francesco Rodeghiero, Marc Michel, Terry Gernsheimer, Marco Ruggeri, Victor Blanchette, James B. Bussel, Douglas B. Cines, Nichola Cooper, Bertrand Godeau, Andreas Greinacher, Paul Imbach, Mehdi Khellaf, Robert J. Klaassen, Thomas Kühne, Howard Liebman, Maria Gabriella Mazzucconi, Adrian Newland, Ingrid Pabinger, Alberto Tosetto and Roberto Stasi

- **Skin**

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Petechiae (does not include steroid–induced or senile purpura)	☐ No	☐ Less than or equal to 10 in a patient's palm-sized area in the most affected body area ☐ Any number if reported by the patient	☐ More than 10 in a patient's palm-sized area or more than 5 in at least 2 patient's palm-sized areas located in at least 2 different body areas, one above and one below the belt (in the most affected body areas)	☐ More than 50, if scattered both above and below the belt	

- **Mucosal**

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Epistaxis*	☐ No	☐ Lasting < 5 min ☐ Any episode if reported by the patient	☐ Lasting > 5 min or interfering with daily activities	☐ Packing or cauterization or in-hospital evaluation at the time of this visit ☐ Medical report describing packing or cauterization or in-hospital evaluation	☐ RBC transfusion or Hb drop > 2g/dL

- **Organ**

	GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT				
	0	1	2	3	4
Hematuria	☐ No	☐ Any episode if reported by the patient ☐ Microscopic (lab analysis)	☐ Macroscopic ☐ Described in a medical report	☐ Macroscopic, and requiring cystoscopy or other therapeutic procedures or in-hospital evaluation at the time of this visit ☐ An equivalent episode if described in a medical report	☐ RBC transfusion or Hb drop > 2g/dL

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HARMONIZATION OF TERMINOLOGY AND DEFINITIONS OF BLEEDING IN ITP

The term **"severe" ITP** should be used only in patients who have **"clinically relevant bleeding"**

The ability to maintain a platelet count sufficient to prevent **"clinically significant bleeding"** could be considered as response to treatment in refractory ITP.

Bleeding manifestation can generally be labeled <u>"severe or clinically relevant"</u> if:

- grade 3 for skin and/or
- grade 2 or higher for mucosal domains and/or
- higher than grade 1 for organ domain
  (S >2 and/or M >1 and/or O >1).

Immune ThrombocytoPenia: ITP

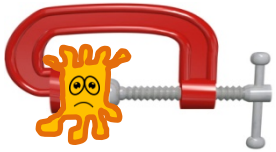
Pathogenetic mechanism

Primary event
Unknown (infections? Molecular mimicry? tissue damage? Genetic predisposition?)

Loss of self-tolerance
Mainly unknown (Treg deficit? Inflammatory cytokines production? Autoimmune mechanism)

Th1 and cytotoxic autoreactive T cells activation
Process speed up (APC potentiation? Lipopolysaccharids release?)

Massive IgG auto antibodies production
Process speed up (APC potentiation? Lipopolysaccharids release?)

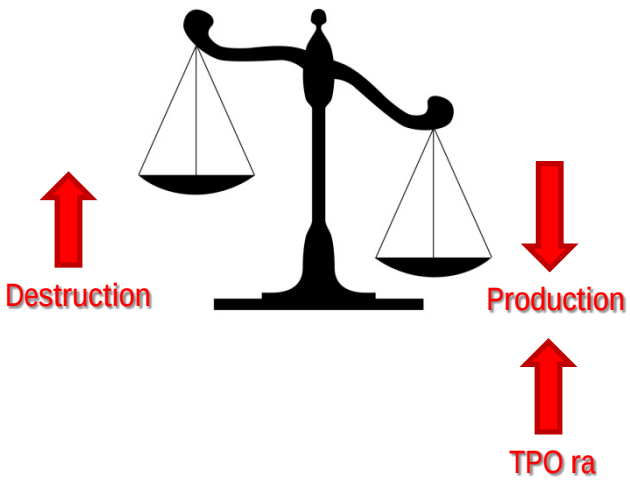


Clinical Manifestations
Megakaryocytes inhibition and platelets distruction

Immune ThrombocytoPenia: ITP

Pathogenetic mechanism

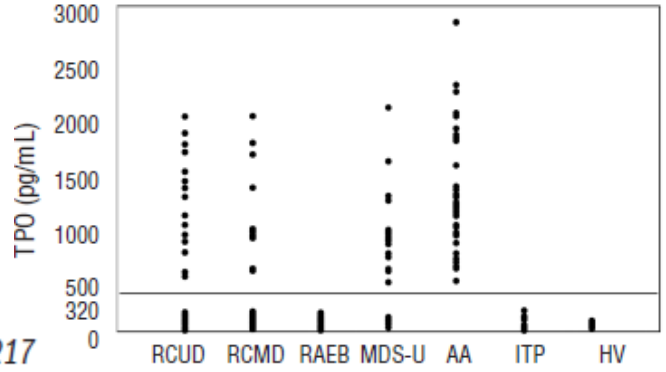
In contrast with the classical view of an increased platelets destruction not compensated by an increased platelets production (kinetic studies with 51Cr).



More recent kinetic analysis showed that platelets production in ITP is normal or reduced.

Therefore the pathogenetic mechanism of ITP is sustained by two factors:

- Increased platelets destruction
- Suppressed platelets production



Increased plasma thrombopoietin levels in patients with myelodysplastic syndrome: a reliable marker for a benign subset of bone marrow failure *Haematologica 2013;98. doi:10.3324/haematol.2012.066217*

Immune ThrombocytoPenia: ITP

Initial evaluation: What to do?



Basic Evaluation	Useful tests	Less useful test
Patient history	Antiplatelet Abs	TPO
Family History	Antiphospholipid Abs	Reticulated PLT
Phisical exam		PaIgG
CBC + reticolocytes	Antinuclear Abs	Bleeding time
Morphology	PCR for CMV ed EBV	Blood platelets kinetic
Immunoglobulines		Serum complement
BMA (selected patients)		
Coombs test		
HIV-HCV-HP		

Immune ThrombocytoPenia: ITP

Differential diagnosis

Basic Evaluation	Peripheral destruction	Reduced production
Pseudo-thrombocytopenia (EDTA-Heparin)	Neonatal alloimmune thrombocytopenia, (NAIT)	Drugs suppression
Platelets aggregation	Post-transfusion purpura (PTP)	Infectious diseases
	Drug-induced thrombocytopenia (DIT)	Alcool
	Antiphospholipid antibody syndrome (APS)	Myelodisplastic syndromes
	Disseminated intravascular coagulation (DIC)	Hematologic neoplasm's
	Thrombotic thrombocytopenic purpura (TTP)	Bone marrow infiltration (other neoplastic diseases)
	Splenic sequestration	Aplastic Anemia
	Cardiovascular diseases	
	Infectious diseases	
	Pregnancy	

Immune ThrombocytoPenia: ITP

Initial treatment: When?

Children

- Generally only if severe hemorrhage is present
- Case-by-case assessment

Adults

- Confirmed platelet count < 20-30 $x10^9/L$
- Significant hemorrhage with any platelets count

Immune ThrombocytoPenia: ITP

Initial treatment: What to do?

Treatment targets

- Resolution and/or prevention of hemorrhagic manifestations
- Rapid platelets number increase
- Complete response or stable clinical response
- Postpone splenectomy
- QOL improvement

- Temporary platelets number increase

Immune ThrombocytoPenia: ITP

Initial treatment

Treatment	Dose and method	Results	Side effects	Notes
Prednisone or prednisolone (standard doses)	1 mg/kg/die orally for 3-4 weeks, than taper	60-80% short term resp. 20% long term resp.	Many	Acceptable toxicity if not administered for more than 5-6 weeks, include tapering
Dexamethasone	Total dose 40 mg orally for 2-4 weeks in 1-4 cycles	80-90% initial response. The response rate does not increase after 4 cycles Possible superiority to standard PDN	Possibly less than standard doses PDN	Generally acceptable toxicity with no more than 3 cycles
High doses Immunoglobulines (IVIg)	400 mg/kg/die for 5 days 1 gr/kg single dose or 2 days	CR in over 80% of cases and R generally last for 2-3-weeks. Loss of efficacy with repeated exposure	Rarely severe related infusion side effects. Very rarely: thrombosis, renal insufficiency	Treatment required only in cases in which a platelet increase is clinically necessary in the first 24-48 hours
Anti-D Immunoglobulines	50-75 µg/kg single dose	As for IVIg	Very rare cases of itravascular hemolysis, DIC and renal insufficiency	Not available in Italy

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2016 127: 296-302
doi:10.1182/blood-2015-07-659656 originally published online October 19, 2015

High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial

Yu Wei, Xue-bin Ji, Ya-wen Wang, Jing-xia Wang, En-qin Yang, Zheng-cheng Wang, Yu-qi Sang, Zuo-mu Bi, Cui-ai Ren, Fang Zhou, Guo-qiang Liu, Jun Peng and Ming Hou

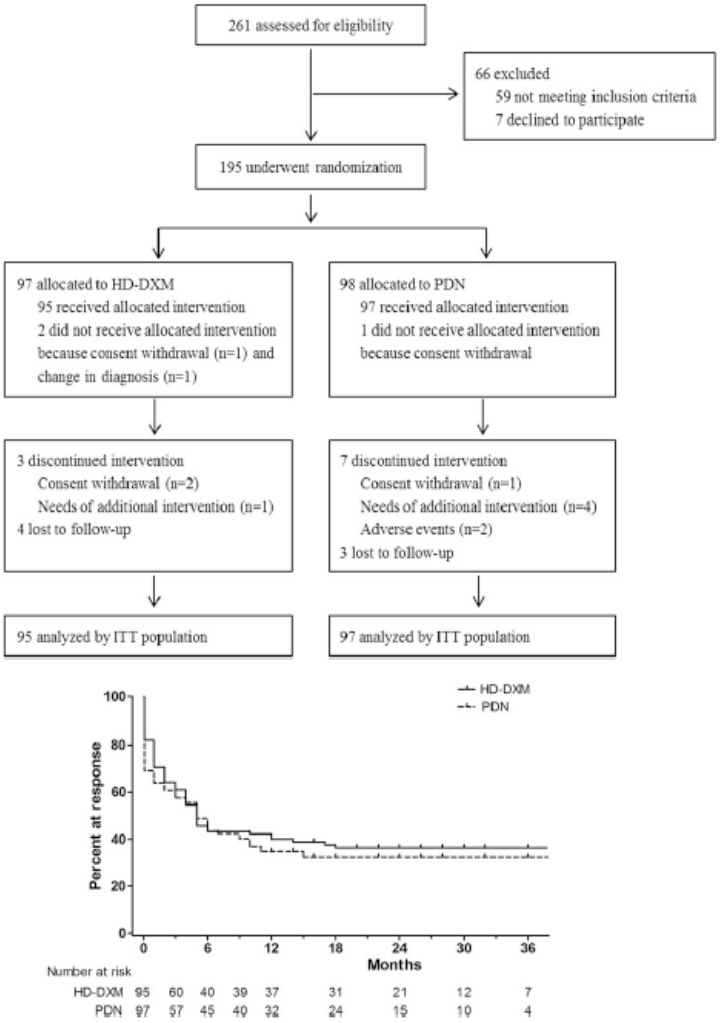

Figure 2. Kaplan-Meier estimates of the duration of response. The Kaplan-Meier curve demonstrated comparable long-term outcomes between the 2 arms ($P = .522$).

In the HD-DXM arm, DXM was administered orally at 40 mg daily for 4 consecutive days and then stopped. If platelet count remained below 30×10^9/L or there were bleeding symptoms by day 10,[7] an additional 4-day course of DXM (40 mg daily) was given.

	HD-DXM (n = 95)	PDN (n = 97)	*P*	OR	95% CI
Overall response, n (%)	78 (82.1)	67 (69.1)	.044	2.054	1.042-4.050
CR, n (%)	48 (50.5)	26 (26.8)	.001	2.789	1.526-5.097
Median TTR, d (range)	3 (1-9)	6 (2-24)	<.001		
SR, n (%)	38 (40.0)	40 (41.2)	.884	0.950	0.534-1.690
Sustained CR, n (%)	26 (27.4)	17 (17.5)	.120	1.773	0.889-3.539

Therefore, HD-DXM could become a preferred corticosteroid approach for first-line management of adult primary ITP. Furthermore, because it has been shown that repeated courses of medication may yield better long-term outcome,[8] future RCTs should be designed to compare the effect of repeated courses vs a limited course of HD-DXM.

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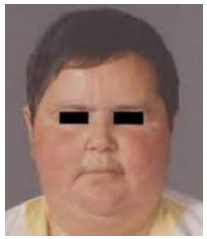
2007 109: 1401-1407
doi:10.1182/blood-2005-12-015222 originally published online October 31, 2006

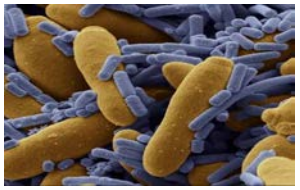
Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience

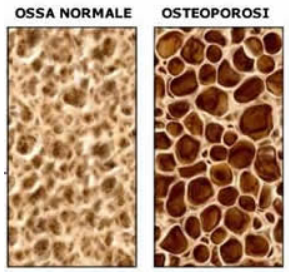
Maria Gabriella Mazzucconi, Paola Fazi, Sayla Bernasconi, Giulio De Rossi, Giuseppe Leone, Luigi Gugliotta, Nicola Vianelli, Giuseppe Avvisati, Francesco Rodeghiero, Angela Amendola, Carlo Baronci, Cecilia Carbone, Stefano Quattrin, Giuseppe Fioritoni, Giulio D'Alfonso and Franco Mandelli

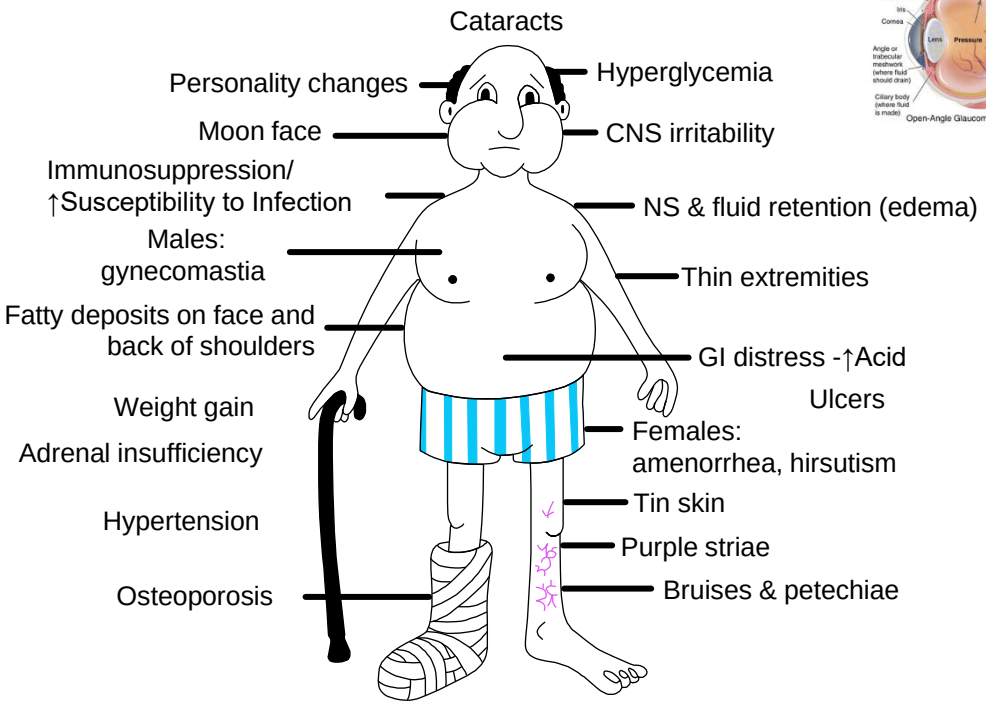
In the GIMEMA multicenter pilot study, oral or intravenous DXM was given as a single daily dose of 40 mg for 4 consecutive days, every 14 days for 4 courses.

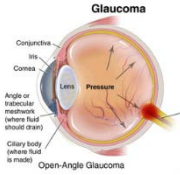
Traditional first-line corticosteroid treatment is limited by **unfavorable AEs**











Unfortunately CS adverse effects rapidly become apparent and create significant complications. With time, the detrimental effects of CS often outweigh their benefits. *(Provan et al. 2010)*

CNS, central nervous system; GI, gastrointestinal; NS, nephrotic syndrome.
Provan D, *et al. Blood* 2010;115:168–186.

Clinical Situation	Therapy Options
First line (initial treatment for newly diagnosed ITP)	Anti-D Corticosteroids: dexamethasone, methylprednisolone, prednis(ol)one IVIg
Second line	Azathioprine Cyclosporin A Cyclophosphamide Danazol Dapsone Mycophenolate mofetil Rituximab Splenectomy TPO receptor agonists (romiplostim and eltrombopag) Vinca alkaloids
Treatment for patients failing first-line and second-line therapies	Category A*: TPO receptor agonists Category B†: alemtuzumab, combination of first-line and second-line therapies, combination chemotherapy, hematopoietic stem cell transplantation

*Sufficient data to support recommendation.
†Minimal data to support recommendation; potential for considerable toxicity.

bunch of keys

door lock

Immune ThrombocytoPenia: ITP

Second line treatment "Splenectomy"

Intervention	Initial response rates	Durability	ASH guidelines	International Consensus
Splenectomy	80%	66%	Recommended *Laparoscopic, vaccinations*	Individual judgment (defer 6-12 mos)
Rituximab	50-60%	20-40%	Not recommended *May be considered for patients at risk of bleeding*	Individual judgment
TPO-R agonists	80%	50-60%	Not recommended *May be considered for patients at risk of bleeding*	Individual judgment (maintenance therapy)
Azathioprine, Cyclosporin A Cyclophosphamide Mycophenolate Other	20-80%	20-40%	Not recommended *May be considered*	Individual judgment (maintenance therapy)

Neunert CE, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117(16): 4190-4207. Provan D et al, International Consensus report on the investigation and management of primary immune thrombocytopenia. Blood

Immune ThrombocytoPenia: ITP

Second line treatment "Splenectomy"

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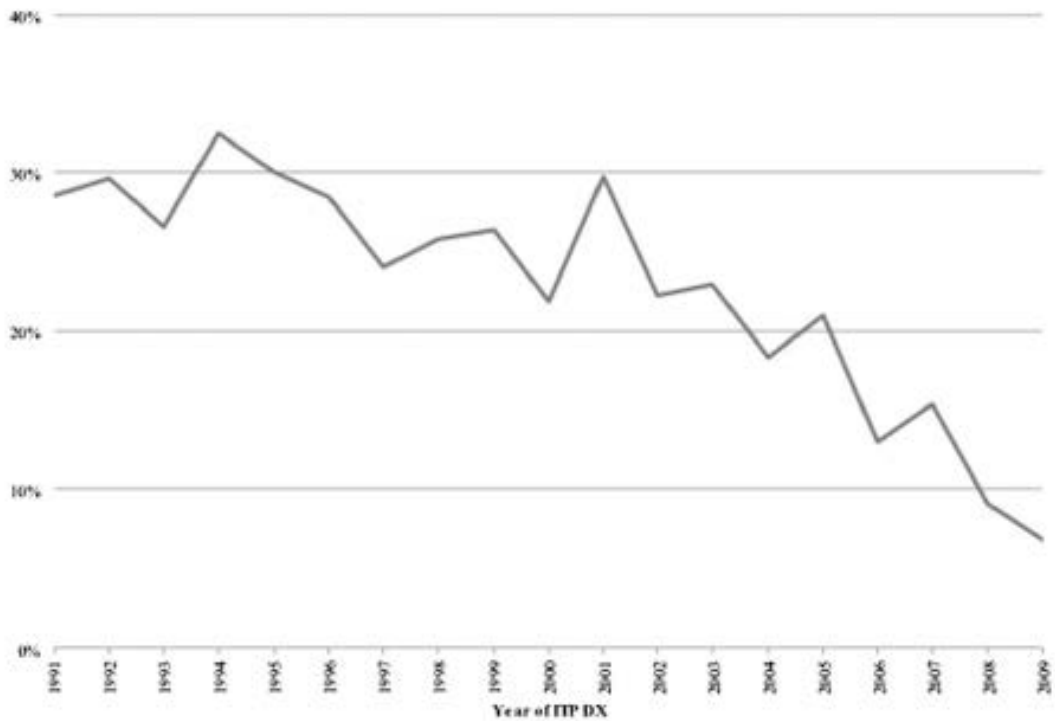
2013 121: 4782-4790
doi:10.1182/blood-2012-12-467068 originally published online May 1, 2013

Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia

Soames Boyle, Richard H. White, Ann Brunson and Ted Wun



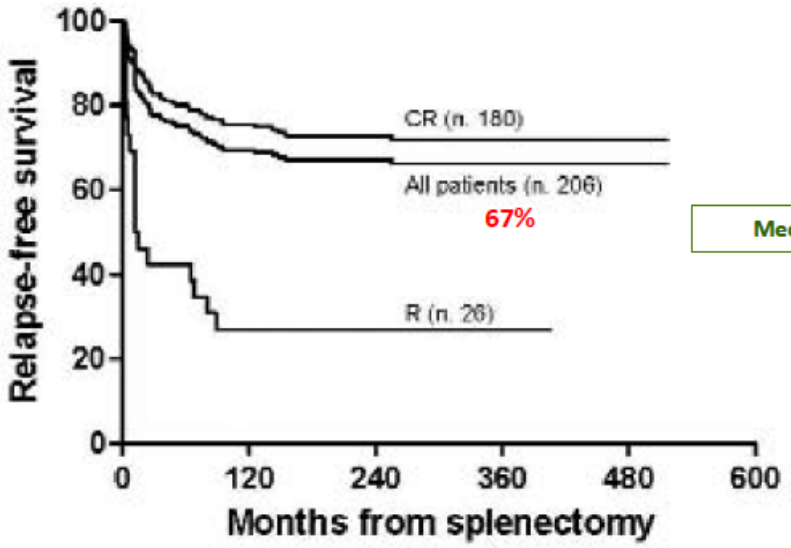
Decline in the rate of splenectomy over time

Immune ThrombocytoPenia: ITP

Second line treatment "Splenectomy"

Splenectomy as a curative treatment for immune thrombocytopenia: a retrospective analysis of 233 patients with a minimum follow-up of 10 years

Nicola Vianelli,[1*] Francesca Palandri,[1*] Nicola Polverelli,[1] Roberto Stasi,[2] Joel Joelsson,[3] Eva Johansson,[3] Marco Ruggeri,[4] Francesco Zaja,[5] Silvia Cantoni,[6] Angelo Emanuele Catucci,[2] Anna Candoni,[5] Enrica Morra,[6] Magnus Björkholm,[3] Michele Baccarani,[1] and Francesco Rodeghiero[4]



Median f-up from splenectomy 20 yrs (10-43)

Figure 1. Relapse-free survival (RFS). RFS was 67% (95% CI: 61.3%-74.1%) for all responding patients, 73% (95% CI: 66.2%-79.5%) for CR patients and 27% (95% CI: 10%-43%) for R patients ($P<0.001$). CR: complete response (PLT>100x10^9/L). R: Response (PLT 30-100x10^9/L).

haematologica | 2013; 98(3)

Splenectomy as a curative treatment for immune thrombocytopenia: a retrospective analysis of 233 patients with a minimum follow-up of 10 years

Vianelli et al.

haematologica | 2013; 98(3)

Table 4. Long-term complications.

	N. of events (%)	All patients (233)	Refractory patients (95)	Stable responders (138)	P
Infections					
Lung	63 (40%)	41 (18%)	23 (24%)	18 (13%)	0.03
Gastrointestinal/ urogenital/skin	41 (26%)	21 (9%)	13 (14%)	8 (6%)	0.06
Other (minor recurrent infections)	53 (33%)	28 (12%)	14 (14.5%)	14 (10%)	0.31
Fatal (sepsis)	2 (1%)	2 (1%)	1 (1%)	1 (0.7%)	1.00
Overall	159 (100%)	73 (31%)	40 (42%)	33 (24%)	0.004
Thrombosis					
Stroke/TIA	4 (15.5%)	4 (2%)	2 (2%)	2 (1.4%)	1.00
DVT/PE	12 (46%)	8 (3.5%)	4 (4%)	4 (2.8%)	0.71
AMI	6 (23%)	6 (2.5%)	4 (4%)	2 (1.4%)	0.22
Fatal (2 strokes + 2 AMI)	4 (15.5%)	4 (2%)	3 (3%)	1 (0.7%)	0.30
Overall	26 (100%)	18 (8%)	10 (10.5%)	8 (6%)	0.21
Hemorrhage					
Grade 1-2	221 (92%)	47 (20%)	41 (43%)	6 (4%)	<0.0001
Grade 3-4	17 (7%)	16 (7%)	13 (14%)	3 (2%)	<0.0001
Fatal (intracranial)	3 (1%)	3 (1.2%)	3 (3%)	0 (0%)	<0.0001
Overall	241(100%)	58 (25%)	49 (51.5%)	9 (6.5%)	<0.0001

TIA: transient ischemic attack. DVT: Deep vein thrombosis; PE: Pulmonary embolism; AMI: acute myocardial infarction.

Immune ThrombocytoPenia: ITP

Second line treatment "Splenectomy"

Clinical Outcome and Predictive Factors in the Response to Splenectomy in Elderly Patients with Primary Immune Thrombocytopenia: A Multicenter Retrospective Study

Park YH et al. Acta Haematologica 2016

Table 3. Response after splenectomy

	Overall (n = 184)	Younger group (n = 132)	Elderly group (n = 52)	p
CR	124 (67.4)	92 (69.7)	32 (61.5)	0.288
R	24 (13.0)	14 (10.6)	10 (19.2)	
NR	33 (17.9)	24 (18.2)	9 (17.3)	
Not available	3 (1.6)	2 (1.5)	1 (1.9)	
Overall response (CR+R)	144 (80.4)	106 (80.3)	42 (80.7)	0.466
Relapse	43 (29.1)	24 (22.6)	19 (45.2)	0.006

Values are n (%).

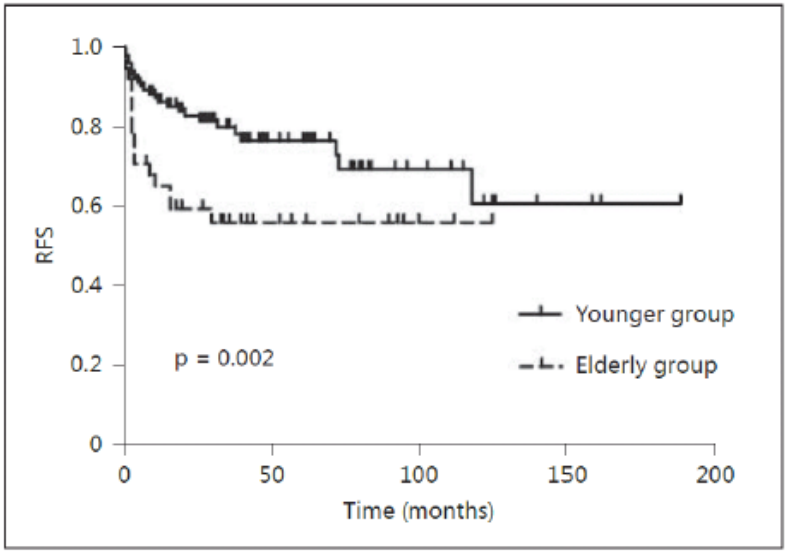


Fig. 3. Kaplan-Meier curve of RFS according to age group.

Table 4. Postoperative complications according to age group

	Overall (n = 184)	Younger group (n = 132)	Elderly group (n = 52)	p
Early complications (within POD 30)	19 (10.3)	9 (6.9)	10 (19.2)	0.013
Bleeding	14 (7.6)	7 (5.3)	7 (13.5)	0.060
Infection	3 (1.6)	1 (0.8)	2 (3.8)	0.036
Cardiovascular event	2 (1.1)	1 (0.8)	1 (1.9)	0.492
Mortality within POD 30	1 (0.5)	0 (0.0)	1 (1.9)	0.110
Late complications (POD 31–100)	16 (8.7)	6 (4.5)	10 (19.2)	0.001
Thrombosis	8 (4.3)	2 (1.5)	6 (11.5)	0.001
Infection	6 (3.3)	4 (3.0)	2 (3.8)	0.382
Bleeding	2 (1.1)	0 (0.0)	2 (3.8)	0.005
RBC transfusions	0 (0–15)	0 (0–15)	0 (0–10)	0.160
Postoperative stay, days	8 (4–60)	7 (4–60)	9.5 (4–52)	0.019

Values are medians (range) or n (%). RBC = Red blood cell.

Immune ThrombocytoPenia: ITP

Second line treatment "Splenectomy"

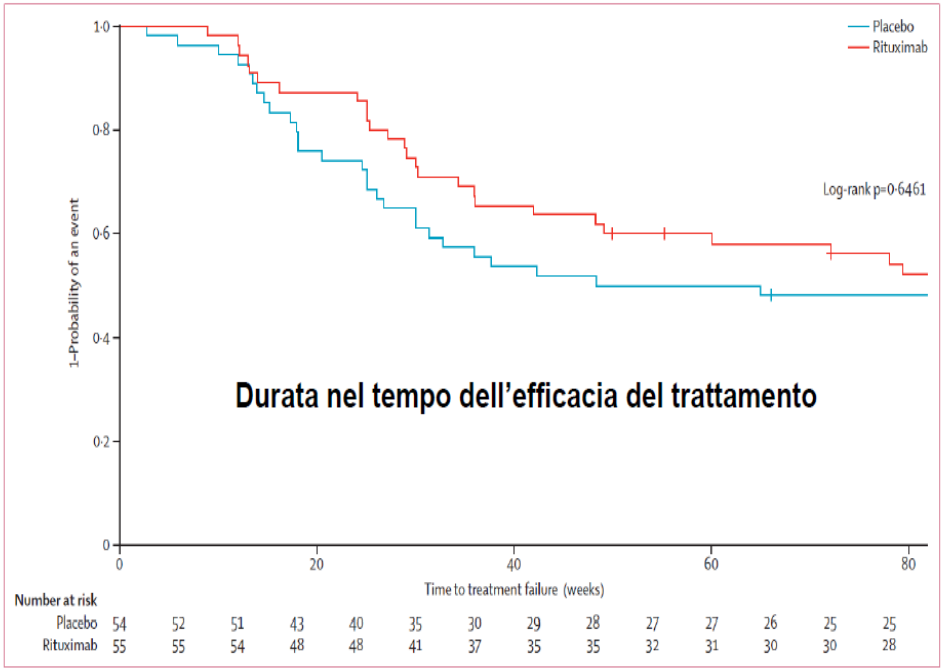
PRO	CONTRA
Best durable response rate	Fear of surgery
Low surgery complications	Fear to remove an "healthy organ"
"Short treatment"	New treatments available
Possible in elderly	Lack of prognostic factors "Leap in the dark"
Acceptable infections risk profile (vaccines, antibiotics)	Lack of perception of a "life treatment"

Immune ThrombocytoPenia: ITP

Second line treatment: Rituximab

Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial

Ghanima W et al. Lancet 2015



	Rituximab (n=55)	Placebo (n=54)	p value*
Efficacy outcomes			
Treatment failure	32 (58%)	37 (68%)	0·65
Splenectomy	8 (15%)	14 (26%)	0·12
Overall response	40 (73%)	36 (67%)	0·15
Loss of overall response	27 (68%)	28 (78%)	0·01
Median duration of overall response (weeks)	36 (13–not reached)	7 (5–69)	0·01
Complete response	28 (51%)	21 (39%)	0·12
Loss of complete response	14 (50%)	13 (62%)	0·19
Median duration of complete response (weeks)	76 (32–not reached)	49 (20–95)	0·19

Figure 3: Time to treatment failure within 78 weeks

The composite outcome of splenectomy or meeting criteria for splenectomy after week 12 if splenectomy was not done because of contraindications or patient's refusal.

Immune ThrombocytoPenia: ITP

Second line treatment: Rituximab

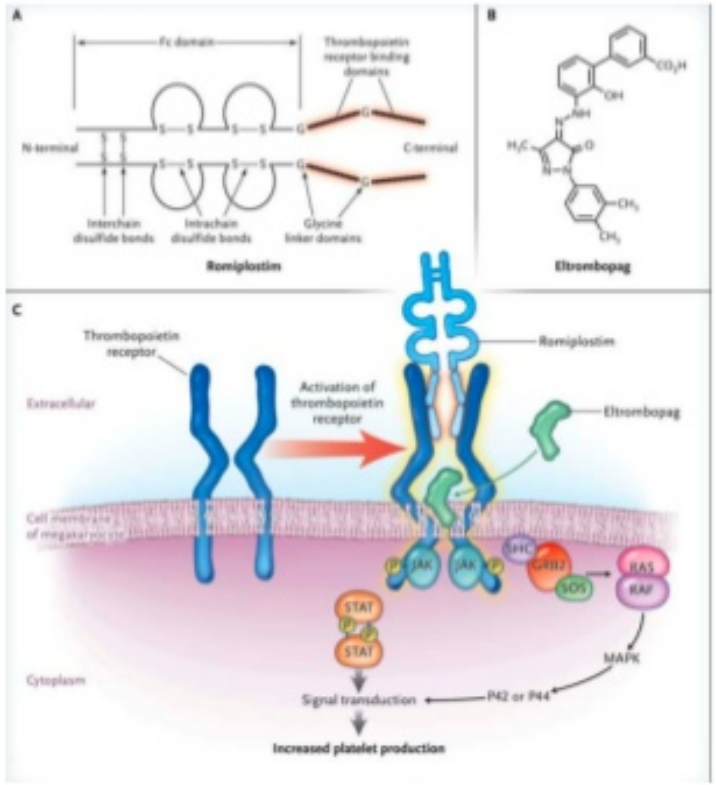
PRO	CONTRA
Possible response	HCV/HBV reactivation
Delay splenectomy	Risk of infections
Acceptable toxicity profile	Low percent of long remission
Possible repeated use	Progressive multifocal leukoencephalopathy (PML)
Acceptable risk profile	Efficacy?
Higher response in females	

Immune ThrombocytoPenia: ITP

Second line treatment: TPOra

Thrombopoietin-Receptor Agonists for Primary Immune Thrombocytopenia
NEJM. 2011

- Eltrombopag
  - Oral thrombopoietin (TPO) receptor agonist
  - Interacts with transmembrane domain of human TPO receptor
  - Induces megakaryocyte proliferation and differentiation from bone marrow progenitor cells
- Romiplostim
  - An Fc-peptide fusion protein (peptibody)
  - Increases platelet production through binding and activation of the thrombopoietin (TPO) receptor – similar mechanism to endogenous TPO



Immune ThrombocytoPenia: ITP

Second line treatment: TPOra

Characteristic	Romiplostim	Eltrombopag
Classification	Peptibody	Nonpeptide small molecule
Indications	Chronic ITP	Chronic ITP Severe aplastic anemia HCV infection–associated thrombocytopenia Chronic ITP in pediatrics older than 6 yrs of age
Delivery/dosing	SC/weekly	PO/daily
TPO receptor binding site	Ligand-binding domain	Transmembrane domain
Rebound thrombocytopenia	4% to 10%	4% to 10%
Elevated transaminases	--	3% to 7%
Myalgias	10%	5%
Marrow fibrosis	MF2: 10% to 70% MF3: 1% to 3%; rare collagen	MF2: 10% to 70% MF3: 1% to 3%; rare collagen

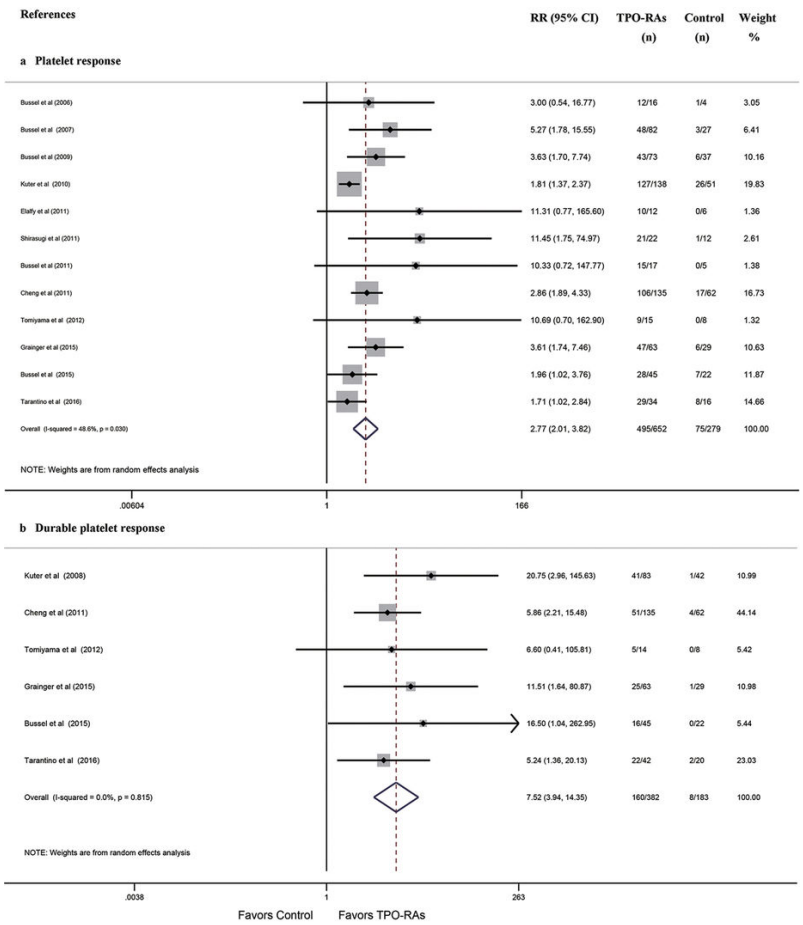
SCIENTIFIC REPORTS

Efficacy and safety of thrombopoietin receptor agonists in patients with primary immune thrombocytopenia: A systematic review and meta-analysis

Published: 19 December 2016

Li Wang[1,2,*]

SCIENTIFIC REPORTS | 6:39003 | DOI: 10.1038/srep39003



Meta-analysis results (13 randomised studies) indicated that TPO-ra:

- Significantly increased rates of R or DR
- Reduced the incidences of any or severe bleeding events.
- TPO-RAs significantly decreased the need for rescue medications
- Increased the patients able to reduce or discontinue concurrent ITP therapies.
- Reduced the incidence of severe AEs in ITP patients.
- The incidence of AEs was similar to that in the placebo groups

Immune ThrombocytoPenia: ITP

Second line treatment: TPOra

PRO	CONTRA
60-80% R or DR rate	Lack of perception of a "life treatment"
Delay splenectomy	Cost
Acceptable toxicity profile	Platelet count fluctuation
Reduce AE	Thrombosis?
Acceptable risk profile	Rebound worsening of thrombocytopenia
QOL	Increased bone marrow reticulin

Immune ThrombocytoPenia: ITP

Second line treatment: TPOra

New possible applications:

- TPO-RA switching
- Sustained remission after stop
- Bridge to Splenectomy
- Bridge to Surgery
- Bridge to Recovery

How to use TPO-ra?

- **Definitive use**
- **Definitive/Temporary use**

  (switch, treatment suspension, …..)

- **Temporary use (“on demand”)**

  (“bridge to splenectomy”, “bridge to recovery”, on-demand, emergency, ……)

Immune ThrombocytoPenia: ITP

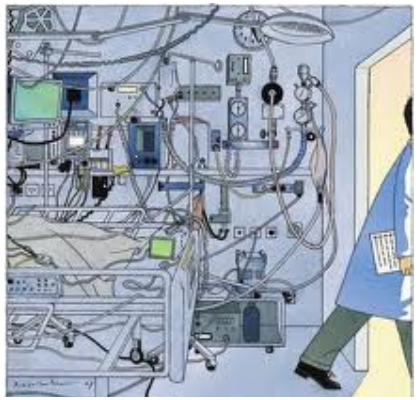
The "Human factor"

"Minimalist approach"

- Few test
- Hemorrhages prevention
- QOL
- Side effect reduction

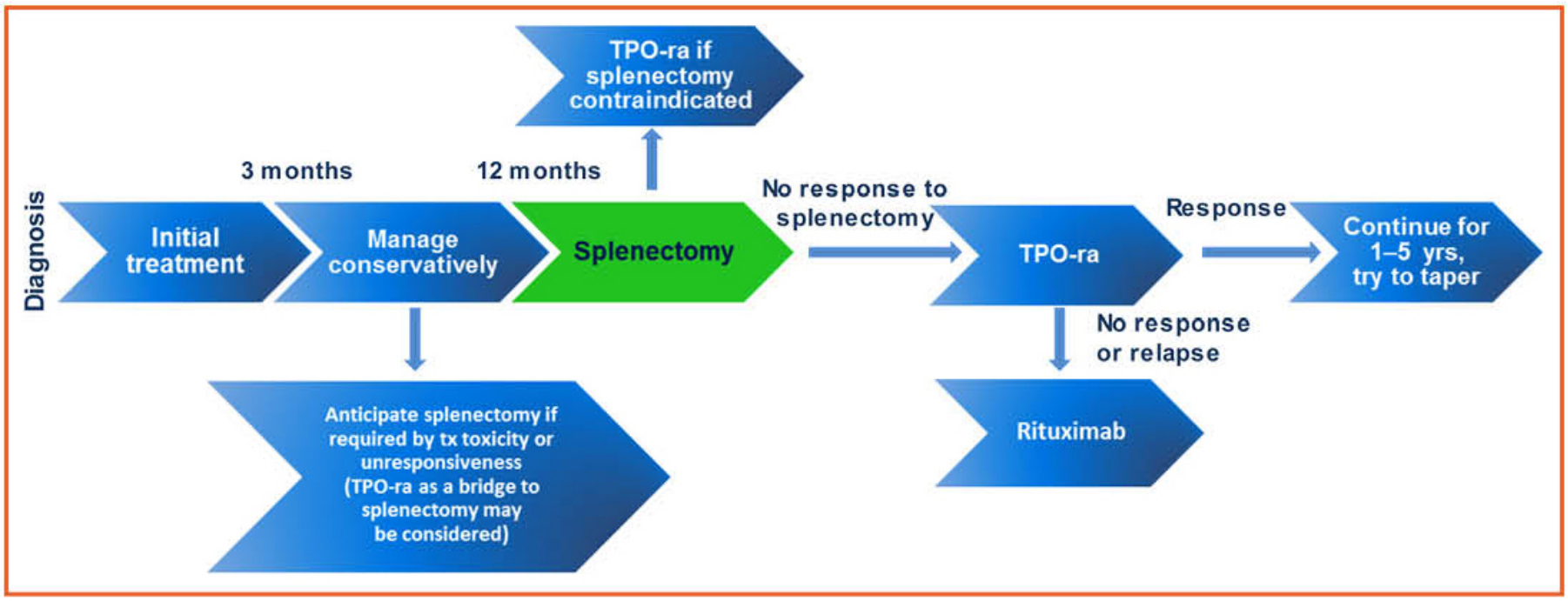
"Intensivist approach"

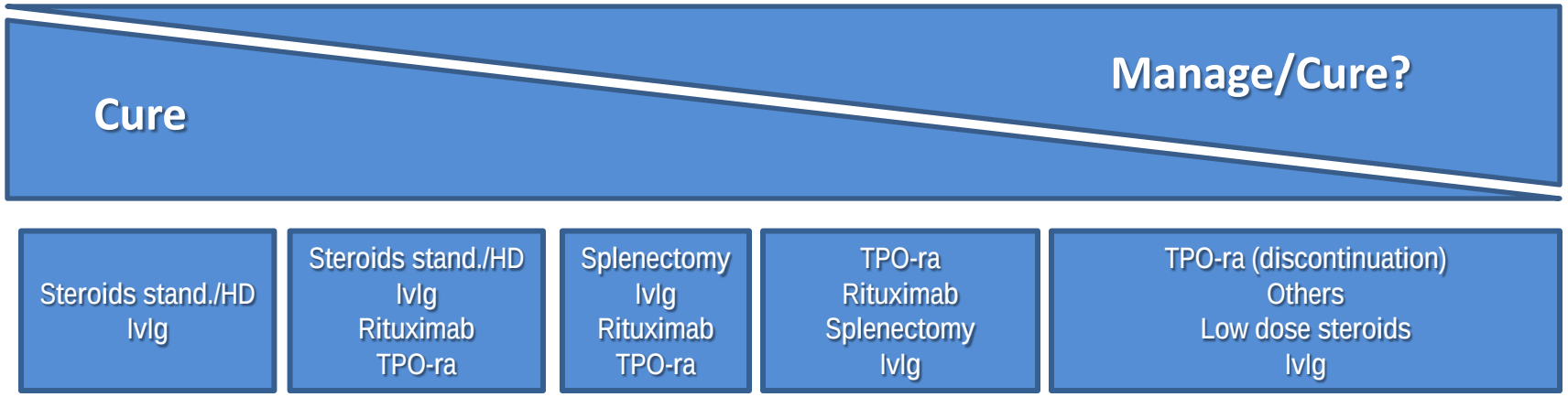
- Complex tests
- More effective treatments
- Aim to cure



Factors which will influence the choice of treatment

- Compliance
- Secondary effects
- Secondary ITP
- Accessibility to the cure
- Hemorrhagic manifestations
- Patient's expectations
- Other treatments
- Activities and life style
- Surgery
- Predisposition to Hemorrhagic or thrombotic events
- Concomitant diseases

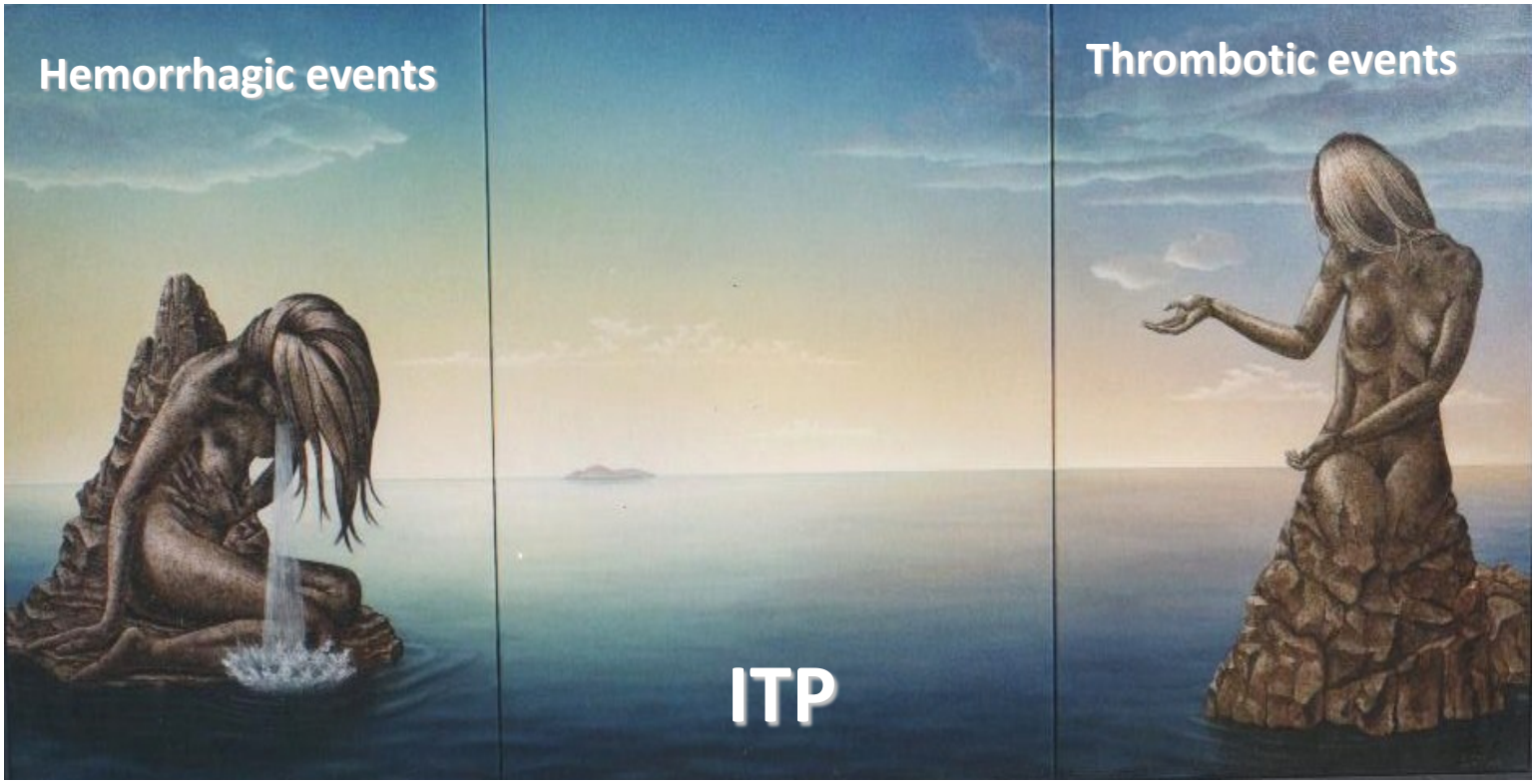

Diagnosis
Initial treatment
3 months
Manage conservatively
12 months
Splenectomy
TPO-ra if splenectomy contraindicated
No response to splenectomy
TPO-ra
Response
Continue for 1–5 yrs, try to taper
No response or relapse
Rituximab
Anticipate splenectomy if required by tx toxicity or unresponsiveness (TPO-ra as a bridge to splenectomy may be considered)


Cure
Manage/Cure?
Steroids stand./HD
Ivlg
Steroids stand./HD
Ivlg
Rituximab
TPO-ra
Splenectomy
Ivlg
Rituximab
TPO-ra
TPO-ra
Rituximab
Splenectomy
Ivlg
TPO-ra (discontinuation)
Others
Low dose steroids
Ivlg

“Just one more thing...”

Immune ThrombocytoPenia: ITP

Is ITP a thrombophilic disorder?



Scylla and Charybdis were mythical sea monsters noted by Homer; Greek mythology sited them on opposite sides of the Strait of Messina between Sicily and the Italian mainland. Scylla was rationalized as a rock shoal (described as a six-headed sea monster) on the Italian side of the strait and Charybdis was a whirlpool off the coast of Sicily.

Michele D'Avenia "Scilla e Cariddi" 2001 olio su tela

Is ITP a thrombophilic disorder?

TABLE I. Annualized Incidence Rates with Their 95% CI and Unadjusted IRR of Arterial Thrombosis and Venous Thromboembolism in Patients with Primary Chronic ITP and in Control Populations

	VTE				AT			
	Incidence × 100 person/ years (95% CI)				Incidence × 100 person/ years (95% CI)			
Reference	Patients	Controls	IRR[a]	*P*	Patients	Controls	IRR[a]	*P*
Sarpatwari et al. (2010) [12]	0.66 (0.45–0.95)	0.42 (0.34–0.53)	1.58 (1.01–2.48)	<0.05	0.96 (0.70–1.29)	0.67 (0.56–0.80)	1.37 (0.94–2.00)	n.s.
Enger et al. (2010) [16]	0.41 (0.26–0.61)	0.09 (0.05–0.14)	2.89 1.33–6.29	<0.05[b]	2.78 (2.34–3.28)	1.78 (1.58–2.00)	1.58 (1.29–1.94)	<0.05[b]
Severinsen et al. (2010) [13]	0.53 (0.29–0.99)	0.20 (0.15–0.29)	2.65 (1.27–5.50)	<0.05				
Nøorgard et al. (2012) [14]					1.14 (0.79–1.63)	0.91 (0.81–1.03)	1.32 (0.88–1.98)	n.s.
Nøorgard et al. (2015) [15]	0.67 (0.46–0.97)	0.28 (0.23–0.34)	2.39[c]	<0.05[b]	1.15 (0.86–1.54)	0.88 (0.79–0.97)	1.30[c]	n.s.

Data refer to true incidence of new events during the observation period.
[a] Adjusted according to different covariates in the different studies, often including age, sex, and/or comorbid status, for example, use of corticosteroids, diabetes, hypertension, splenectomy (see original articles).
[b] *P* at least less than 0.05, based on CI of IRR, no exact value provided in the articles.
[c] Unadjusted, no IRR provided in the article, significance cannot be derived for AT but is apparent from VTE, based on the CI of incidence.

- **The risk for VTE is higher** (around 2 times) in chronic ITP compared with controls.
- **The increased risk is more evident in older than 50s–60s,** but again the studies have no power to show significant differences according to age subgroups.
- For **AT there is a trend for increased risk** in patients with chronic ITP, but statistical significance was not reached in three of the four studies

F. Rodeghiero. American Journal of Hematology, Vol. 91, No. 1, January 2016

Do TPOra further increase the Thrombotic Risk?

TABLE II. Annualized Incidence Rates of Arterial and Venous Thrombosis and Crude Percentages Derived From Industry-Sponsored Studies on TPO-ra

	Romiplostim (all studies) [33]	Romiplostim (long-term study) [34]	Eltrombopag [35]	Eltrombopag[a] [36]
Number of patients with TEEs	39/653 (5.9%)	19/291 (6.5%)	16/299 (5.3%)	19/302 (6.3%)
Mean exposure time (years)	1.41	2.11		2.35 (median)
Total number of TEEs	69	25	20	26
Arterial	26	16		
Venous	40	9	9	12
Others	3		11	14
First TEE rate per 100 patient-years[b]	4.2	3.10		
All TEE rate per 100 patient-years[b]	7.5	4.16	3.2	2.53
Arterial	2.8	2.6		
Venous	4.3	1.5		

[a] Data from Saleh updated to February 2013.
[b] Rates were calculated on the average exposure time, without censoring patients with first thomboembolic events.

- The annualized risk for VTE appears four to five times higher and that for AT **at least twice compared with that experienced in ITP patients not exposed to these.**
- **The high rate of thrombosis found in patients exposed to TPO-ra may be due to the prospective nature of these investigations and to the stricter monitoring required.**

F. Rodeghiero. American Journal of Hematology, Vol. 91, No. 1, January 2016

Is ITP a thrombophilic condition?

- The clinician facing a new patient with ITP requiring treatment should be aware that there is **a slightly increased risk of VTE**, not demanding special attention and follow-up.
- **Particularly in patients aging more than 60 years** with additional risk factors any effort should be made to improve modifiable personal risk factors
  - **Treatment** (corticosteroids, estroprogestinic preparation)
  - **Associated conditions** (atrial fibrillation, diabetes mellitus, hypercholesterolemia, treated hypertension, valvular or coronary disease)
  - **Life style** (Smoking, obesity, immobilization)
- **Prophylaxis for thrombosis should be done** in ITP patients in risky situations like immobilization and surgery (including splenectomy).

Where is the ITP target?

or

The “Mini Principle”

Minimal amount of medication to maintain
Minimal platelets count that result in
Minimal bleeding and
Minimal side effects

Our job?

- Examine
- Consider
- Explain
- Listen
- Suggest

and then

- Prescribe

“I need something to make me feel better. Can you prescribe a Ferrari?”