2021

Progetto Ematologia Romagna

Come usare gli agonisti del recettore della trombopoietina

Elena Rossi

Fondazione Policlinico Gemelli-IRCCS-UCSC Roma

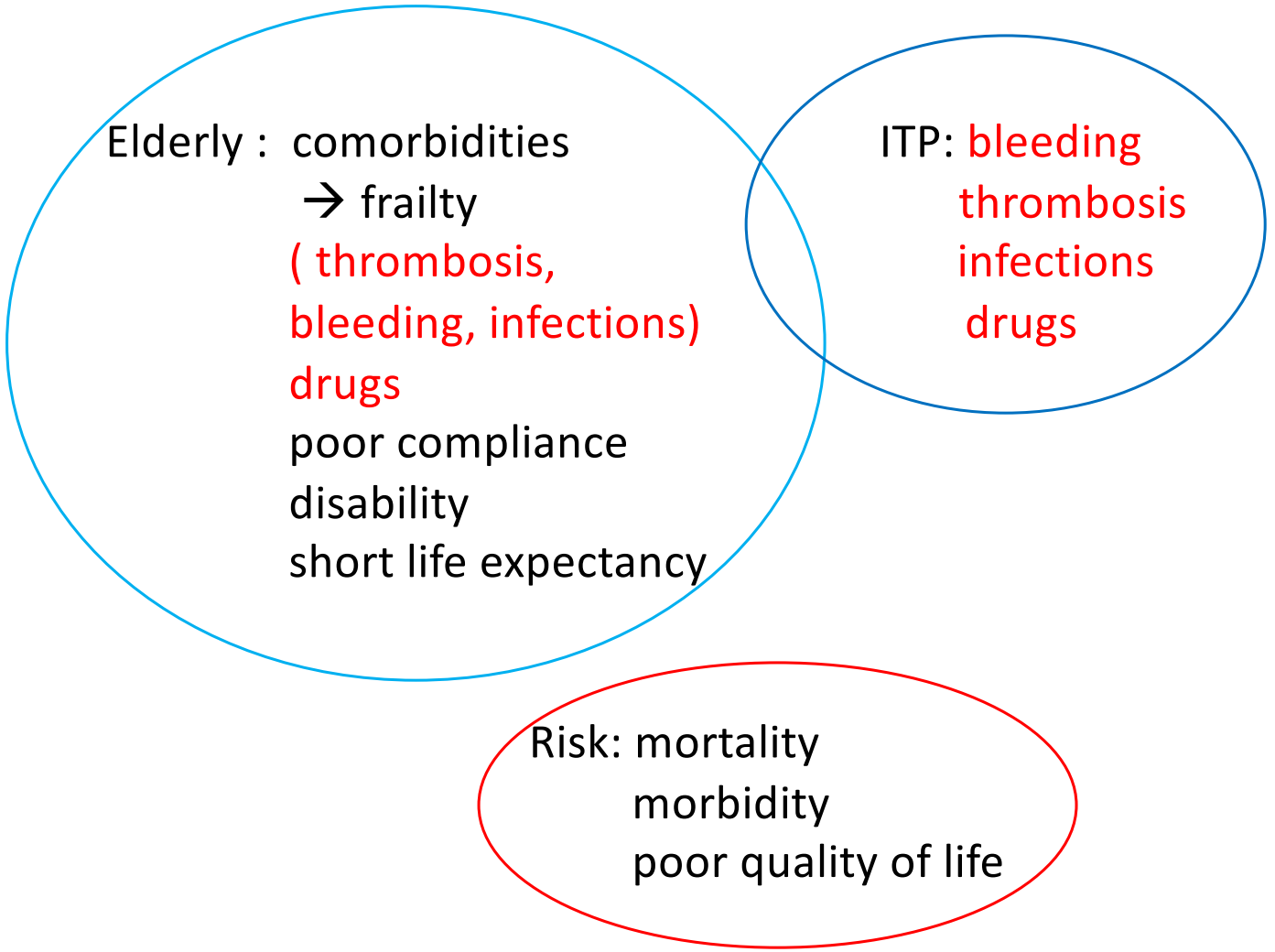
Il relatore ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18,19 dell'Accordo Stato-Regione del 19 aprile 2012

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Amgen-Novartis

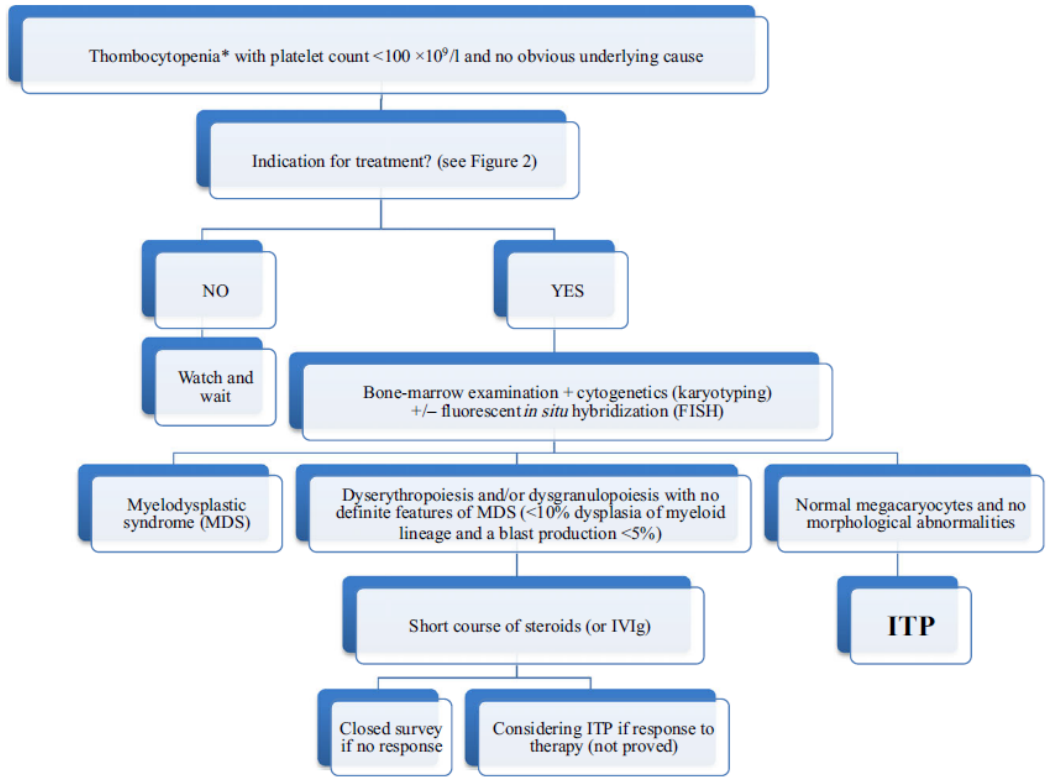
ITP in ELDERLY: key words



ITP in ELDERLY: diagnosis

How is ITP diagnosed in the elderly?

Primary ITP is defined as an autoimmune disorder characterized by an isolated platelet count <100 × 10^9/l, in the absence of any underlying cause or disorder (Cines & Blanchette, 2002; Rodeghiero *et al*, 2009). According to most guidelines, diagnosis is based on history, physical examination, complete blood count and examination of peripheral blood smears, which should exclude other causes of thrombocytopenia (British Committee for Standards in Haematology General Haematology Task Force, 2003; Cines & Bussel, 2005; Rodeghiero *et al*, 2009; Provan *et al*, 2010; Neunert *et al*, 2011). There is no specific recommendation for the diagnosis of ITP in older patients, but some points should be considered. Drug-induced ITP, caused by drug-dependent antibodies that bind to platelets, should be particularly considered in older adults who are frequently taking poly-medications. The more frequent sources of drug-induced ITP are listed in Table I (George & Aster, 2009; Reese *et al*, 2010; Garbe *et al*, 2012). Five to seven days of drug exposure are usually needed to produce sensitization, so drug exposure in the weeks preceding the occurrence of thrombocytopenia must be carefully searched. Arnold *et al* (2013) proposed an approach to the diagnosis and management of new-onset thrombocytopenia suspected to be drug-induced ITP by using an algorithm based on the chronology and severity of the thrombocytopenia and severity of bleeding.



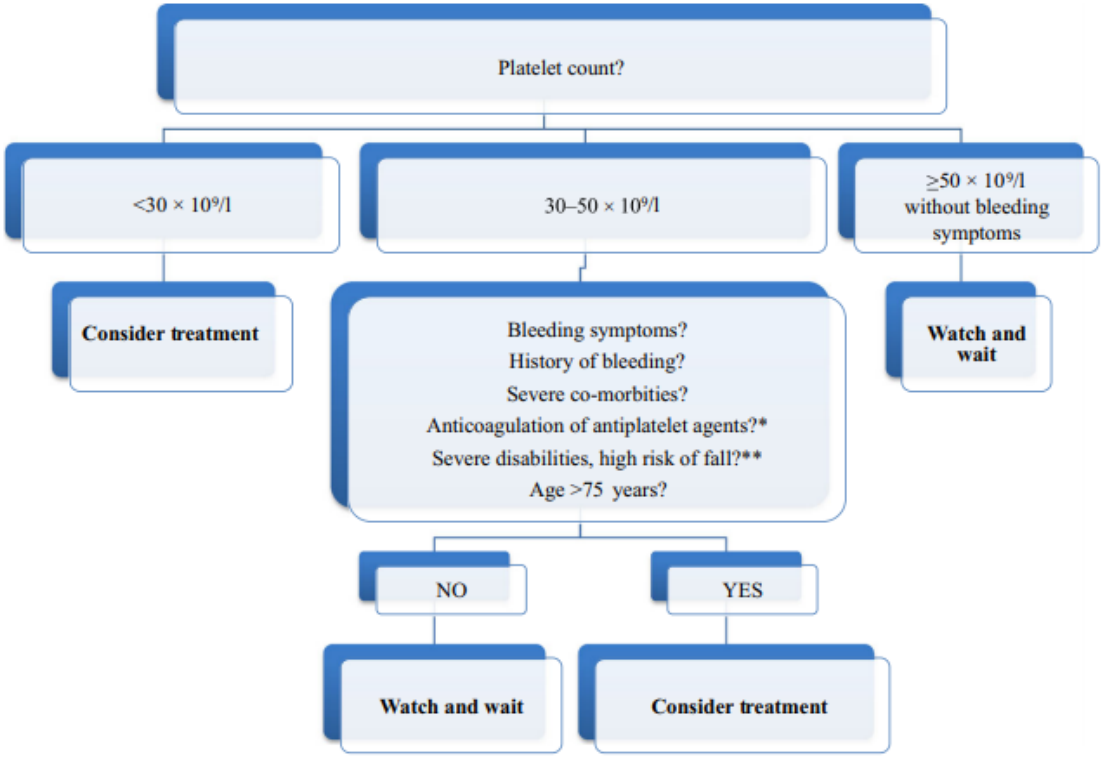
*: isolated thrombocytopenia including normal peripheral blood smear findings, absence of other cytopenia, normal mean corpuscular volume (MCV) of red blood cells (<100 fl). If thrombocyopenia is not isolated, consider bone-marrow examination.
Abbreviations: ITP: immune thrombocytopenia; IVIg: intravenous immunoglobulin

Fig 1. How to diagnose ITP in elderly patients.

Mahevas M. BJH review. 2016

How we manage immune thrombocytopenia in the elderly

Who should be treated?



*: Discuss the possibility of stopping the treatment with the cardiologist or the neurologist according to the indication
**: Consider geriatric evaluation

https://onlinelibrary.wiley.com/doi/pdf/10.1111/bjh.14067

Mahevas British Journal of Haematology, 2016, 173, 844–856

What are the factors associated with the choice of second-line therapy?

Table II. Proposals for treating immune thrombocytopenia (ITP) in elderly patients.

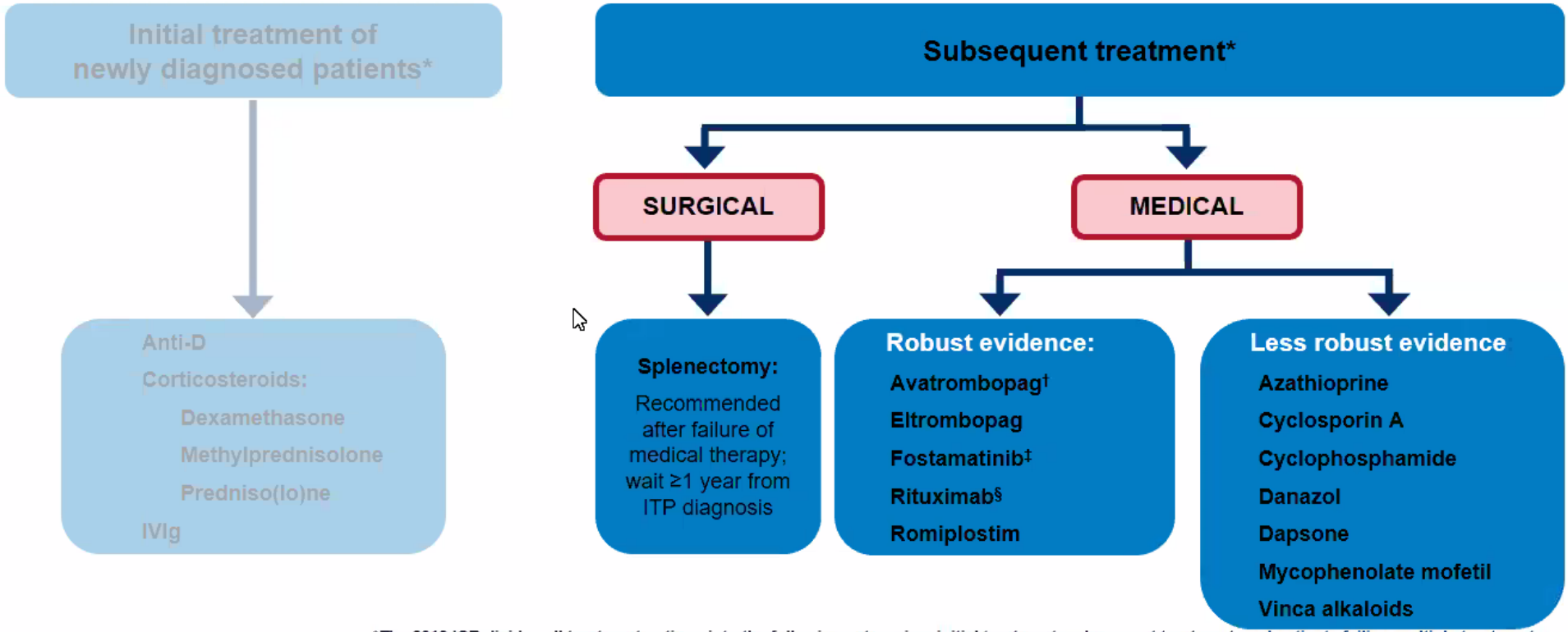
First-line therapy Short course of prednisone or dexamethasone ± intravenous immunoglobulin (IVIg) 0·4-0·5 g/kg body weight for 4-5 days (IVIg reserved for patients with severe bleeding)				
If relapse after stopping steroids or no response to first -line therapy, consider second-line therapy				
Second-line therapy options: choice based on the factors to consider				
Factors to consider	**Second-line options**			
	Splenectomy	**Rituximab***	**TPO-RAs**	**Dapsone*, danazol***
Health funding authorities' restriction of the use of TPO-RAs/rituximab	PROs	**CONs**	**CONs**	
Patient and physician preference	PROs	PROs	PROs	PROs**
Newly diagnosed or persistent ITP (chronic <1 year)	**CONs**			
Severe co-morbidities	**CONs**		PROs	
Severe cognitive impairment			Use romiplostim as a priority for better compliance	
Poor life expectancy	**CONs**		PROs	
History of severe infection, hypogammaglobulinaemia, previous prolonged treatment with steroids or immunosuppressive drugs	AVOID	AVOID	PROs	
History of thrombosis	AVOID	PROs	AVOID	AVOID for danazol
Splenic destruction of platelets in isotopic study if available*	PROs			

* off-label use ** for patients with minor or no bleeding manifestations (avoid danazol in men with a history of prostate cancer)
ITP, immune thrombocytopenia; TPO-RAs, thrombopoietin-receptor agonists

CONs	Second-line treatment is contraindicated according to the factor in the same row in the left column
PROs	Second-line treatment is a good option according to the factor in the same row in the left column
AVOID	Second-ine treatment is not the best option but is not strictly contraindicated according to the factor in the same row in the left column
	The factor in the same row in the left column has no influence on the choice of the second-line treatment

Mahevas M. BJH review. 2016

ICR 2019
Overview of second-line therapies for adult ITP



***The 2019 ICR divides all treatment options into the following categories: initial treatment, subsequent treatment, and patients failing multiple treatments.**
†Approved in the USA for thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure, and thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment; approved in the EU for severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure. ‡Approved in the USA for thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment; approved in the EU for chronic ITP in adults who are refractory to other treatments; **§Rituximab is not approved for the treatment of ITP.**

Provan D, et al. Blood Adv 2019;3:3780–817.

Adult ITP
Subsequent treatment in chronic and persistent ITP[1]

Medical therapies with robust evidence

1. **TPO-RAs (eltrombopag, avatrombopag, romiplostim) have provided excellent responses (>60%) in splenectomized and nonsplenectomized patients***
   - **Response to continued TPO-RAs persists for up to 6–8 years and often allows other ITP therapy to be reduced or discontinued**
   - **Cessation of treatment will lead to the return of thrombocytopenia in most cases, but some patients (10–30%) may achieve a durable response after TPO-RAs are tapered and withdrawn**
2. Evidence from a systematic review of multiple uncontrolled trials and RCTs shows a response to rituximab in 60% of patients. Long-term durable responses occur in 20–25% of adult patients.† Prior to treatment, hepatitis B status should be determined, and vaccination against encapsulated gram-positive bacteria should be given‡
3. Fostamatinib offers an alternative mechanism for reducing platelet destruction. It may provide response rates of 43% but stable responses of only 18%[2§]

RCT, randomized controlled trial; TPO-RA, thrombopoietin receptor agonist.
*Grade A recommendation, evidence level Ib. †Grade B recommendation, evidence level IIa. ‡Grade C recommendation, evidence level IV. §This recommendation is based on evidence from 2 double-blind RCTs in patients who had failed splenectomy, TPO-RAs, and/or rituximab, and with a median duration of ITP of 8.5 years. Fostamatinib was given at an initial dose of 100 mg twice daily, and frequently increased to 150 mg twice daily in nonresponders.

1. Provan D, et al. Blood Adv 2019;3:3780–817; 2. Bussel J, et al. Am J Hematol. 2018;93:921–30.

ITP IN ADULTS: second line therapy

In adults with ITP ≥3 months who are corticosteroid-dependent or unresponsive to steroids, should splenectomy, rituximab or TPO-RAs be used?

- Goal of treatment: to achieve a sustained increase in platelet count considered hemostatic for an individual patient, minimize adverse events and possibly achieve remission[1]
- In practice, decision usually considers all 3 options but evidence only available for dichotomous comparison with placebo/standard of care
- Preference to ***avoid splenectomy*** in patients with diagnosis <12 months, due to possibility of disease remittance
- Choice of therapy also influenced by factors not captured in clinical trials
  - Patient-specific: age, co-morbidities, bleeding risk
  - Disease-specific: ITP duration, response/side effects to previous treatments
  - **Patient preference and values**

Neunert C et al, Blood Advances 2019

ITP IN ADULTS: second line therapy

Summary

- Evaluated second-line therapy in adults including splenectomy, rituximab and TPO-RA
- Consider efficacy (durable response), safety and patient's values and preferences
  - Avoiding surgery – TPO-RA or rituximab
  - Avoiding long-term medication – splenectomy or rituximab
  - Achieving durable response – splenectomy or TPO-RA
- **There is no single second-line treatment that is optimal for all patients with ITP. Choice of treatment based on patient and disease related factors**

Neunert C et al, Blood Advances 2019

What are the factors associated with the choice of second-line therapy?

Conclusions

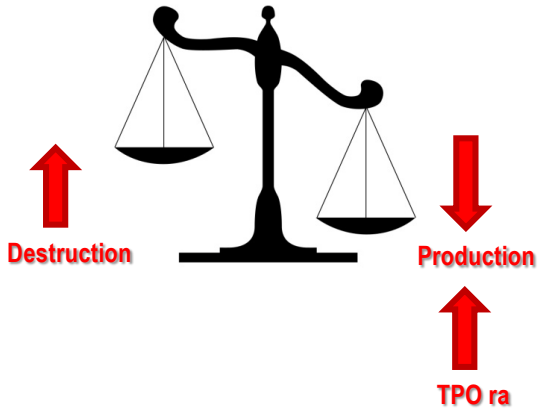
ITP in older patients is an increasing and challenging medical situation. Increased risk of bleeding, comorbidities, possible presence of impairment of cognitive performance or poor life expectancy and, sometimes, reduced tolerance to therapy can affect the therapeutic strategy, which differs from guidelines for younger patients. Unfortunately, recommendations are currently based on expert opinion, and studies focusing on older patients are lacking. We propose an algorithm for treatment, but further studies are required to better delineate and validate these propositions.

Mahevas M. BJH review. 2016

Immune ThrombocytoPenia: ITP

Pathogenetic mechanism

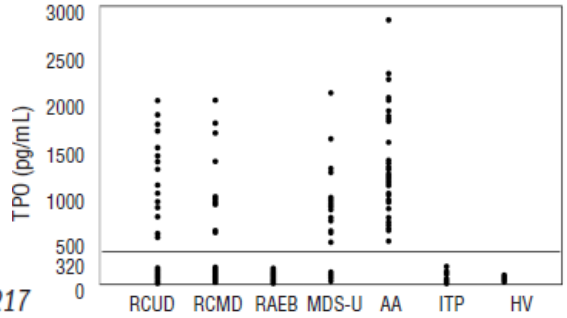
In contrast with the classical view of an increased platelets destruction not compensated by an increased platelets production (kinetic studies with 51Cr).



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

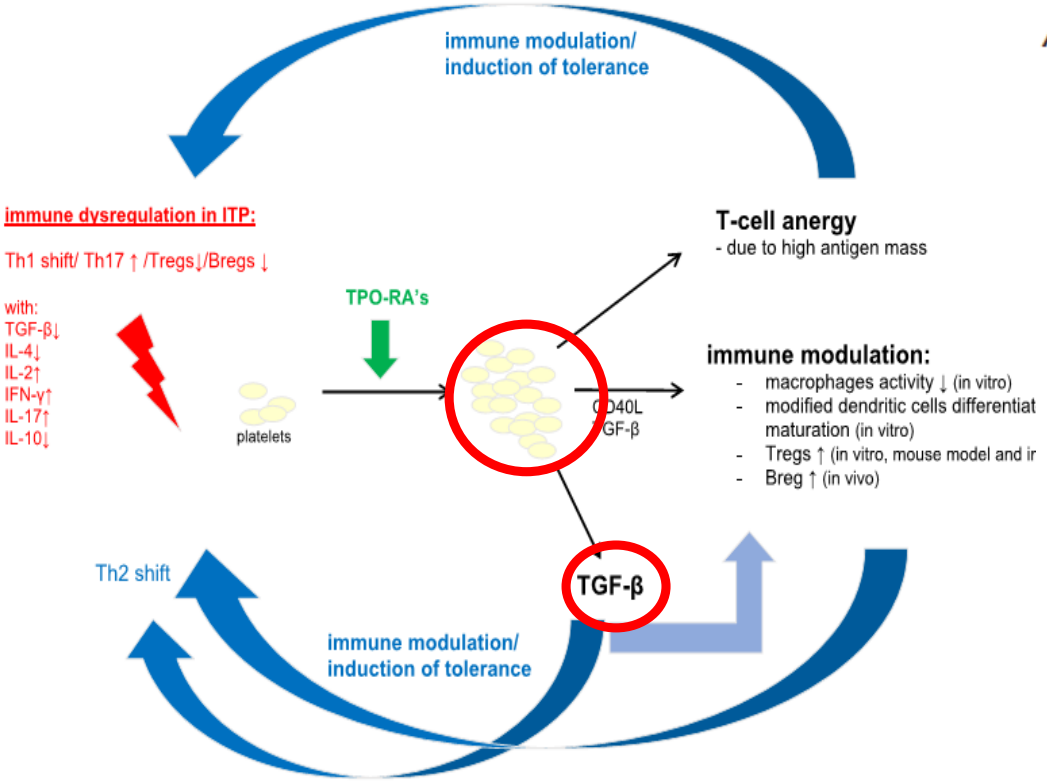


Increased plasma thrombopoietin levels in patients with myelodysplastic syndrome: a reliable marker for a benign subset of bone marrow failure *Haematologica 2013;98. doi:10.3324/haematol.2012.066217*

Thrombopoietin receptor agonists: a new immune modulatory strategy in immune thrombocytopenia?

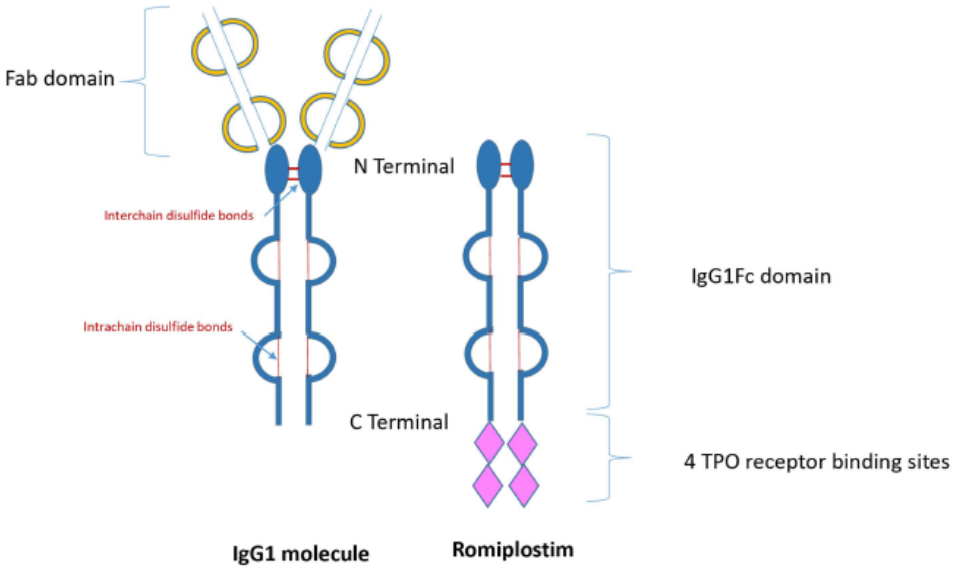
Alexandra Schifferli*, Thomas Kühne

Seminars in Hematology 53 (2016) S31–S34



Immunomodulation in Primary Immune Thrombocytopenia: A Possible Role of the Fc Fragment of Romiplostim?

Alexandra Schifferli[1], Falk Nimmerjahn[2] and Thomas Kühne[1]*



Silvia Cantoni, ASST Niguarda, Milano, 2020

Front Immunol 2019;10:art 1196

Trombopoietina e TPO RAs

Trombopoietina

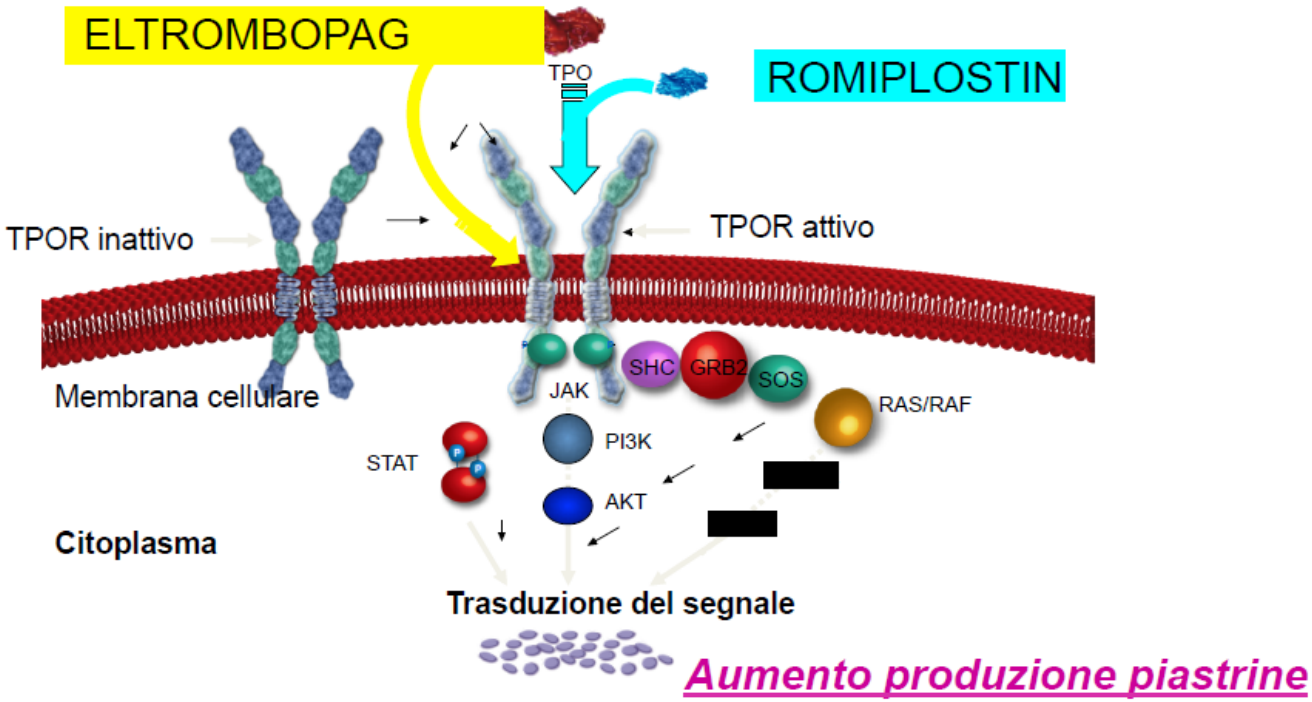
- Prodotta dal fegato
- Principale regolare di megacariocitopoiesi e produzione piastrinica
- Il livello di TPO circolante in forma libera (attiva) dipende dalla quantita' variabilmente legata a i recettori Mpl presenti sulla membrana di megacariociti e piastrine.

	Eltrombopag	Romiplostim
Tipo di molecola	▪ Piccola molecola sintetica ▪ Agonista orale non-peptidico del TPO - R[1,2]	▪ Agonista peptidico del TPO-R, via sottocutanea[1,] ▪ Possibile comparsa di anticorpi anti RMPL
Sito di legame (MoA)	▪ Si lega ad un dominio transmembrana del TPOR diverso dal sito di legame della TPO[1–3]	▪ Si lega al dominio extracellulare come la TPO endogena[5]
Competizione con la TPO endogena?	No[1-3]	Si[5]
Trasduzione del segnale	▪ Differente meccanismo di trasduzione del segnale rispetto alla TPO[2,6]	▪ Stimola una via di segnalazione simile a quella della TPO,[1] che è in grado di innescare l'attivazione piastrinica[7]

1. Evangelista M, et **al.** ***Curr Drug Discov Technol*** **2007; 4: 162–73; 2. Stasi R, et al.** ***Drugs*** **2008; 68(7): 901–12; 3. Erickson-Miller CL, et al.** ***Exp Hematol*** **2005; 33(1): 85–93; 4. Bussel JB, et al.** ***N Engl J Med*** **2007; 357(22): 2237–475; 5.Broudy V, Lin N.** ***Cytokine*** **2004; 25(2): 52–60; 6. Erhardt JA, et al.** ***Exp Hematol*** **2009 Jul 23 [Epub ahead of print]; 7. Kuter DJ.** ***Annu Rev Med.*** **2009;60:193-206.**

Meccanismo d'azione di eltrombopag e romiplostin

Non contengono sequenza aminoacidica o una struttura molecolare presente nella TPO endogena, pertanto escludibile che l'insorgenza di Ab anti contro TPO mimetici possa neutralizzare la TPO endogena



La scelta del TPO-mimetico

Eltrombopag	Romiplostim
Somministrazione orale	Somministrazione subcutanea
Dose iniziale 50 mg/die (poi tra 25-75 mg/die)	Necessità di titolare il dosaggio (1-10 mcg/kg sc /sett)
Assumere almeno a 4 ore di distanza dai cibi contenenti cationi polivalenti, prodotti caseari, antiacidi	Nessuna interazione con il cibo
Leggera nausea e vomito, cataratta, alterazioni cutanee	Lievi artralgie, vertigini, insonnia, mialgia, dolore alle estremità, dolore addominale, dispepsia, anticorpi anti TRA
Anormalità epatobiliari	Nessuna anormalità epatobiliare

Interazione con statine

Entrambi i TPO hanno profili di efficacia e sicurezza convincenti come si evince dagli studi registrativi e di estensione, in termini di:

- INCREMENTO DELLA CONTA PIASTRINICA
- RIDUZIONE DEGLI EVENTI EMORRAGICI
- RIDUZIONE DELLA NECESSITA' DI TERAPIE DI SALVATAGGIO
- RIDUZIONE DELLA NECESSITA 'DI TERAPIE CONCOMITANTI
- DURATA DELLA RISPOSTA
- SCARSA INCIDENZA DI EFFETTI COLLATERALI
- MIGLIORAMENTO DELLA QUALITA'DELLA VITA

TPO-ra and the elderly: recommendations

- Eltrombopag should be taken away from the meals or drugs that could compromise its absorption.
- Romiplostim requires nursing skills (sc injection) that the elderly patients or their caregivers may not have.
- Both drugs require health care. A particular surveillance is necessary with elderly patients

TPO-RA (agonisti recettore trombopoietina)

Trattamento di 1° scelta per ITP cronica e persistente (durata almeno 6 mesi)

- incrementano le piastrine nel 70-80% dei pazienti (>90% a breve termine)
- risposta dopo 1-2 settimane di terapia
- risposta mantenuta nel 40-50% dei pazienti
- efficaci con o senza splenectomia e a tutte le eta'
- non c'è cross reattivita'
- riducono eventi emorragici e necessita' di trattamenti in emergenza
- migliorano la qualita' di vita nella ITP cronica (circa il 50% sospendono CS)

Potenziali rischi: rebound della piastrinopenia dopo sospensione, eventi tromboembolici (non confermato dai trials), fibrosi midollare (2-11% in genere lieve, asintomatica e reversibile)

Uso ottimale del TPO-RA in 2° linea

- Minima dose efficace a mantenere adeguata conta piastrinica e prevenire i sanguinamenti. Se plt >50.000/mcL per lungo periodo, iniziare tapering

- Pazienti che non tollerano o non rispondono a un TPO-RA possono fare lo switch.

- Evitare interruzioni e/o eccessivi aggiustamenti della dose: possono causare fluttuazioni piastrniche (piu' comuni nello splenectomizzato)

- Elevata efficacia, buona tollerabilita', bassa tossicita'. Adatti per terapia a lungo termine nella PTI cronica

(10-30% dei pazienti possono mantenere una risposta a lungo termine dopo sospensione della terapia)

Serious non bleeding toxicities

	ROMIPLOSTIM			ELTROMBOPAG		
	Active arm N=100	Placebo N= 46	Extension N= 291	Active arm N=314	Placebo N= 137	Extension N= 299
Toxicites	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Class-specific toxicites						
Bone marrow fibrosis	1(1)	0	9(3)	0	0	8(3)
Thrombosis	2 (2)	2(4)	**17 (6)**	1 (0.3)	0	**13(4)**
Rebound thrombocytopenia	13 (13)	NR	NR	20 (6)	10 (7)	14 (5)
Hematologic malignancy	0	0	1 (0.3)	0	0	1 (0.3)
Romiplostim-specific toxicites						
Neutralizing antibody formation	0	0	2	NA	NA	NA
Eltrombopag-specific toxicites						
Hepatotoxicity	0	0	NR	33(11)	9(7)	24(8)
Cataract	NA	NA	NA	5(2)	2(1)	NR

Cuker A, Sem Hematol 2010

"Watch and rescue" or chronic treatment?

a US **cost consequence model** showed that from a payer perspective TPO-RA use may significantly reduce the overall management costs of non-splenectomized patients with chronic ITP compared with a watch-and-rescue approach

	Romiplostim	Eltrombopag	"Watch and rescue"
Drug acquisition cost	$44,321	$37,033	0
Drug administration cost	$600	0	0
Physician visit and platelet count monitoring cost	$711	$711	$711
Liver function monitoring cost	0	$77	0
Average number of BREs	1.03	1.40	2.74
Cost of BREs	$6,164	$8,418	$16,464
Total cost	$51,796	$46,239	$17,175
Overall response rate	87.8%	71.8%	14.5%
Cost per response	$58,990	$64,432	$118,314

Li X et al, Blood 2015

Efficacy and Safety of Eltrombopag in Elderly Patients with Chronic Immune Thrombocytopenia: Analysis of Five Clinical Trials

Study	Age Group		
	18–49	50–64	≥65
TRA100773A, n[a]	15	9	3
TRA100773B, n[a]	40	15	19
RAISE, n	75	44	16
REPEAT, n[b]	25	20	7
EXTEND, n[c]	148	102	49

2 https://ashpublications.org/blood/article/118/21/3294/69408/Efficacy-and-Safety-of-Eltrombopag-in-Elderly

3

Olney Blood (2011) 118 (21): 3294.

Efficacy and Safety of Eltrombopag in Elderly Patients with Chronic Immune Thrombocytopenia: Analysis of Five Clinical Trials

- Retrospective analysis by age of 446 adult chronic ITP pts receiving eltrombopag in **5 clinical trials**
- 3 placebo-controlled studies (TRA100773A/B, RAISE); 1 open-label study with pts treated intermittently in 3 cycles of up to 6 weeks (REPEAT); and 1 ongoing extension study (EXTEND) of 299 pts who completed a prior eltrombopag trial
- **Thromboembolic events** were reported in 4 (2%), 5 (3%), and 7 **(9%)** pts aged 18–49, 50–64, and **≥65**.
- Proportions of **liver enzymes** elevation and **bone marrow reticulin** grade ≥2 were **similar across age groups.**
- **Bleeding serious AEs** (SAEs) were reported in 7% of pts aged 18–49 and 50–64, and **3%** of pts ≥65.
- **Conclusion: No significant difference in the safety or efficacy profile of eltrombopag was observed for elderly versus younger pts**, although elderly pts seemed to exhibit slightly more robust responses and slightly more non hemorrhagic AEs (including thrombosis), which are not unexpected in an elderly population.

https://ashpublications.org/blood/article/118/21/3294/69408/Efficacy-and-Safety-of-Eltrombopag-in-Elderly

Olney Blood (2011) 118 (21): 3294.

The use of TPO-RAs in ITP: a “real life” retrospective multicenter experience of the Rete Ematologica Pugliese (REP)

First experience in Italy «real life» in unsplenectomized patients

	Romiplostim		Eltrombopag	
n (%)	55	(44.3 %)	69	(55.6 %)
Age, mean (range)	64	(30–88)	67	(30–92)
Sex, M/F	26/29		33/36	
<60 years, # (%)	23	(41.8 %)	31	(44.5 %)
Time of diagnosis	1989–2014		1988–2014	
<2 years from diagnosis	26	(47.2 %)	45	(65.2 %)
Major bleedings	4	(7.3 %)	7	(7 %)
Minor bleedings	12	(21.8 %)	18	(26.1 %)
Median plts before TPO-RAs (range)	17×10×9/L	(1–30)	16×10×9/L	(1–30)

https://link.springer.com/article/10.1007/s00277-015-2556-z

Mazza Ann Hematol (2016) 95:239–244

The use of TPO-RAs in ITP: a “real life” retrospective multicenter experience of the Rete Ematologica Pugliese (REP)

First experience in Italy «real life» in unsplenectomized patients

- overall response rate 80 % (44/55) for romiplostim and 94.2 % (65/69) for eltrombopag;
- duration of response and time to response similar (p = NS).
- response rate to both drugs in non-splenectomized higher than that of splenectomized (p < 0.05).
- Thrombotic events most consistent adverse events recorded in 2 and 3 % of patients treated by romiplostim and eltrombopag, respectively.

Conclusion: romiplostim and eltrombopag are effective in the majority of patients with chronic ITP who failed several lines of therapy; whether TPO-RAs could substitute splenectomy is under discussion and studies are warranted

https://link.springer.com/article/10.1007/s00277-015-2556-z

Mazza Ann Hematol (2016) 95:239–244

Efficacy and safety of the thrombopoietin receptor agonist romiplostim in patients aged ≥65 years with immune thrombocytopenia

- Retrospective analysis
- Data from 3 studies (N = 159; 24.5% ≥65 years of age) analyzed for **efficacy.**
- Data from 13 studies (N = 1037; 28.4% ≥65 years of age) analyzed for **adverse events (AEs).**
- **Slightly higher platelet response** rates were seen among romiplostim-treated **patients ≥65 versus** <65 years.
- The risks for grade ≥3 bleeding (RR 1.92; 95% CI, 0.47–7.95) and thromboembolic events (RR 3.85; 95% CI, 0.53–27.96) were numerically but not significantly higher for romiplostim versus placebo/SOC in patients ≥65 years.
- **Romiplostim is effective and, with the exception of non significant trends showing increased risks of grade ≥3 bleeding and thromboembolic events (a trend observed in other studies), generally well tolerated in older patients with ITP.**

https://link.springer.com/article/10.1007/s00277-015-2485-x

Michel Ann Hematol (2015) 94:1973–1980.

Efficacy and safety of the thrombopoietin receptor agonist romiplostim in patients aged ≥65 years with immune thrombocytopenia

Duration-adjusted rates and relative risks (romiplostim versus placebo/SOC) of adverse events by age

	Aged ≥65 years		Aged <65 years	
	Romiplostim (n=270) 404.0 pt-years	Placebo/SOC (n=42) 37.9 pt-years	Romiplostim (n=701) 1076.9 pt-years	Placebo/SOC (n=91) 70.9 pt-years
AEs, n (r)				
Any AE	4500 (1113.9)	397 (1046.8)	11,994 (1113.8)	839 (1183.4)
RR (95% CI)	1.06 (0.96–1.18)		0.94 (0.88–1.01)	
SAEs	383 (94.8)	56 (147.7)	512 (47.5)	51 (71.9)
RR (95% CI)	0.64 (0.48–0.85)		0.66 (0.50–0.88)	
Treatment-related SAEs	38 (9.4)	12 (31.6)	80 (7.4)	6 (8.5)
RR (95% CI)	0.30 (0.16–0.57)		0.88 (0.38–2.01)	
Fatal events	27 (6.7)	5 (13.2)	12 (1.1)	3 (4.2)
RR (95% CI)	0.51 (0.20–1.32)		0.26 (0.07–0.93)	
Treatment-related fatal AEs	3 (0.7)	0	2 (0.2)	0
RR (95% CI)	—		—	
AEs of interest, n (r)				
Grade ≥3 bleeding events	41 (10.1)	2 (5.3)	132 (12.3)	17 (24.0)
RR (95% CI)	1.92 (0.47–7.95)		0.51 (0.31–0.85)	
Thromboembolic events	41 (10.1)	1 (2.6)	42 (3.9)	5 (7.1)
RR (95% CI)	3.85 (0.53–27.96)		0.55 (0.22–1.40)	
Bone marrow reticulin events[a]	4 (1.1)	0	13 (1.3)	1 (1.4)
RR (95% CI)	—		0.94 (0.12–7.20)	
Bone marrow collagen events[a]	0	0	1 (0.1)	0
RR (95% CI)	—		—	

https://link.springer.com/article/10.1007/s00277-015-2485-x

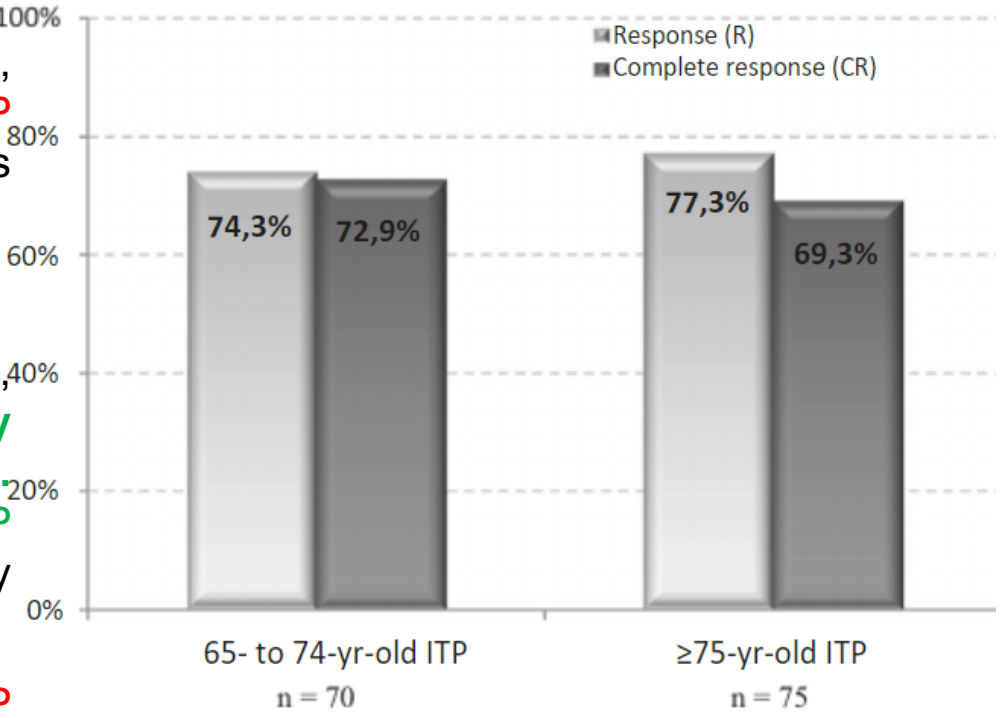
Michel Ann Hematol (2015) 94:1973–1980.

Use of eltrombopag for patients 65 years old or older with immune thrombocytopenia

Spanish real life experience

- A total of 106 primary ITP patients (16 newly diagnosed , 16 persistent, and 74 chronic ITP) and 39 secondary ITP patients (20 to immune disorders, 7 to infectious diseases, and 12 to lymphoproliferative disorders (LPD).
- Median age 76
- Sixty-three adverse events (AEs), mainly grade 1-2, occurred. The most common were **hepatobiliary laboratory abnormalities (HBLAs) and headaches.** One transient ischemic attack in a newly diagnosed ITP and two self-limited pulmonary embolisms in secondary ITP were the only thrombotic events observed.

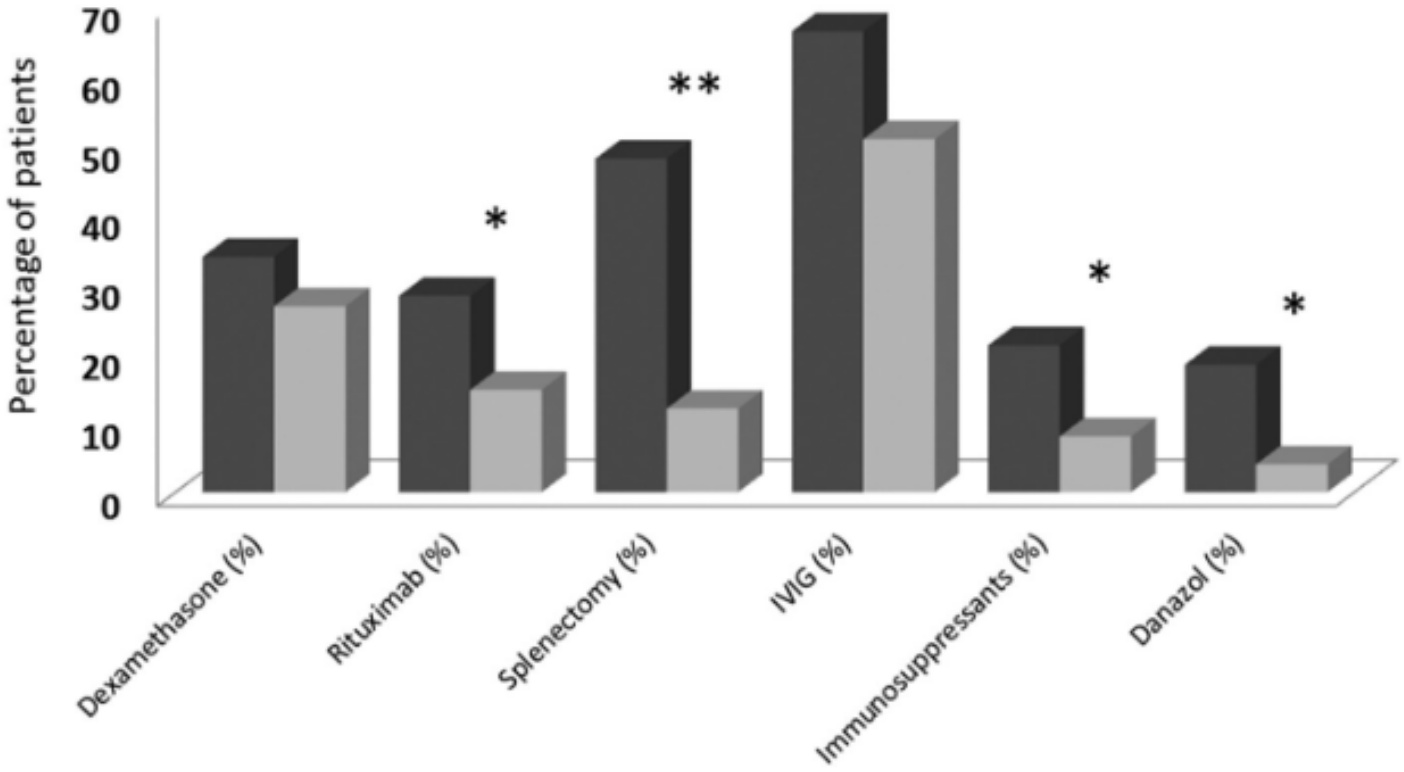
Conclusion: Eltrombopag showed efficacy and safety in ITP patients aged ≥65 years with primary and secondary ITP. However, efficacy results in LPD-ITP were poor. A relatively high number of deaths were observed



Gonzalez Lopez Eur J Haematol. 2020;104:259–270.
https://onlinelibrary.wiley.com/doi/10.1111/ejh.13370

A decade of changes in management of immune thrombocytopenia, with special focus on elderly patients

Use of the various second line therapies according to the date of diagnosis. Dark grey bars indicate percentage of patients diagnosed in the pre-2010 exposed to the specific approach, and lightgrey bars those diagnosed in the post-2010 period.
Immunosuppressive agents include azathioprine, cyclophosphamide, or cyclosporine. *IndicatesP< 0.05; **indicatesP< 0.001.



https://www.sciencedirect.com/science/article/pii/S1079979620304563

Lozano Blood Cells, Molecules, and Diseases Volume 86, February 2021, 102505.

A decade of changes in management of immune thrombocytopenia, with special focus on elderly patients

- 121 adult patients (> 65 years, n = 54; younger individuals, n = 67) who initiated treatment with TPO-RA retrospectively studied.
- **Patients older than 65 years treated with TPO-RA presented at diagnosis with significantly higher platelet counts, less bleeding, and a more prothrombotic profile than younger ones.**
- The high efficacy rates of TPO-RA, preferentially used during the last decade in non-chronic phases, precluded from further therapies in the majority of ITP patients.
- Their administration was associated with a sharp decline in the last decade in the use of splenectomy and intravenous immunoglobulin, especially in younger ITP individuals.

Conclusion **preferential use of TPO-RAs in elderly ITP patients** with fewer bleeding complications but more unfavorable prothrombotic conditions than in younger individuals

https://www.sciencedirect.com/science/article/pii/S1079979620304563

Lozano Blood Cells, Molecules, and Diseases Volume 86, February 2021, 102505.

Management of immune thrombocytopenia in elderly patients

- Increased risk of bleeding, thrombosis and infections,
- Often required many concomitant therapies, including antiplatelet or anticoagulant agents, and the treatment-related toxicities are often increased and sometimes more dangerous that the disease itself.
- Not dedicated guidelines, and only a few specific studies.
- TPOra prominent drug in this subset, even if they are associated with a possible increased risk of thrombosis, and long-term toxicity is unknown
- Other drugs, such as dapsone and danazol, have a well-known efficacy and safety profile, and still represent a valid option

https://www.sciencedirect.com/science/article/pii/S0953620518303662

Elisa Lucchini Renato Fanin Nichola Cooper Francesco Zaja European Journal of Internal Medicine 58 (2018) 70–7674

ITP in the elderly:
Thrombosis during treatment with TPOra

Authors	TPOra	N° patients	Age	VTE
Olney et al, ASH 2011	Eltrombopag	94	≥65	7 (9%)
Michel et al, Ann Hematol 2015	Romiplostim	270	≥65	41 VTEs in 40 pts (14,8%) 10.1/100 pt-yr
Gonzalez-Lopez et al, Eur J Haematol 2019	Eltrombopag	106	≥65	1 TIA (0.9%)
Palandri et al, Thromb Research 2019	Eltrombopag Romiplostim	134	≥60	11 (8.2%); no impact of TPO-RA 1.5/100 pt-yr (data not published)
Castelli R. et al, J Thromb and Thrombolysis 2020	??	80	≥65	10% (all VTE); significant difference in comparison to other 80 pts not treated with TPO-RA (2.5%)
Lozano ML. et al. Blood cells Mol and Dis 2020	Eltrombopag Romiplostim	54	>65	14.8% (VTE 11.1%/Arterial 5.6%); No significant difference if compared to younger pts

Management of elderly patients with immune thrombocytopenia: Real-world evidence from 451 patients older than 60 years

Patients' characteristics and treatment requirement. *P* values refer to comparisons between patients after stratification according to age at diagnosis. CCI: age-adjusted Charlson Comorbidity Index. Previous thromboses include acute myocardial infarction, transient ischemic attack/stroke, superficial/deep vein thrombosis, and acute/chronic arterial obstructive disease.

Patients characteristics	All patients [n. 451]	age 60–74 [n. 258]	age ≥ 75 [n. 193]	*P*
Male sex, no (%)	191 (42.4%)	101 (39.2%)	90 (46.6%)	0.11
Platelet count at ITP diagnosis, x10^9/l, median (range)	16 (1–99)	15 (1–99)	20 (1–99)	0.11
Hemoglobin at diagnosis, g/dl, median (range)	13.4 (10–18)	13.7 (10–18)	13 (10–17)	< 0.001
Leukocyte count at ITP diagnosis, x10^9/l, median (range)	6.7 (1.6–30)	6.7 (1.6–30)	6.5 (1.9–17)	0.20
Haemorrhage any grade at ITP diagnosis, no.	237 (53.9%)	126 (50.4%)	111 (58.4%)	0.09
Grade 3–4, no. (%)	33 (7.3%)	14 (5.6%)	19 (10.0%)	0.07
Platelet count at start of therapy, x10^9/l, median (range)	14 (1–78)	13 (1–78)	16 (1–69)	0.16
ITP therapy, incidence rate per 100 patient-years:				
Second-line	39.2	39.3	39.1	0.97
Third-line	48.7	44.5	59.8	0.08
Time to first line > 1 year, no (%)	81 (17.9%)	40 (15.5%)	41 (21.2%)	0.12
Median age-adjusted CCI value (range)	4 (2–16)	3.5 (2−12)	5 (2–16)	< 0.001
CCI ≥5	214 (47.5%)	89 (34.5%)	125 (64.8%)	< 0.001
Patients with at least one cardiovascular risk factor, no (%)	340 (75.4%)	174 (67.4%)	167 (86.0%)	< 0.001
Patients with previous thrombosis, no. (%)	122 (27%)	54 (20.9%)	68 (35.2%)	0.001
Antiplatelet therapy, no. (%)	95 (21.1%)	49 (19.0%)	46 (23.8%)	0.21
Anticoagulant therapy, no. (%)	37 (8.20%)	13 (5.04%)	24 (12.4%)	0.005

https://www.sciencedirect.com/science/article/pii/S0049384819305201

F Palandri Thrombosis Research 185 (2020) 88–9590

Management of elderly patients with immune thrombocytopenia: Real-world evidence from 451 patients older than 60 years

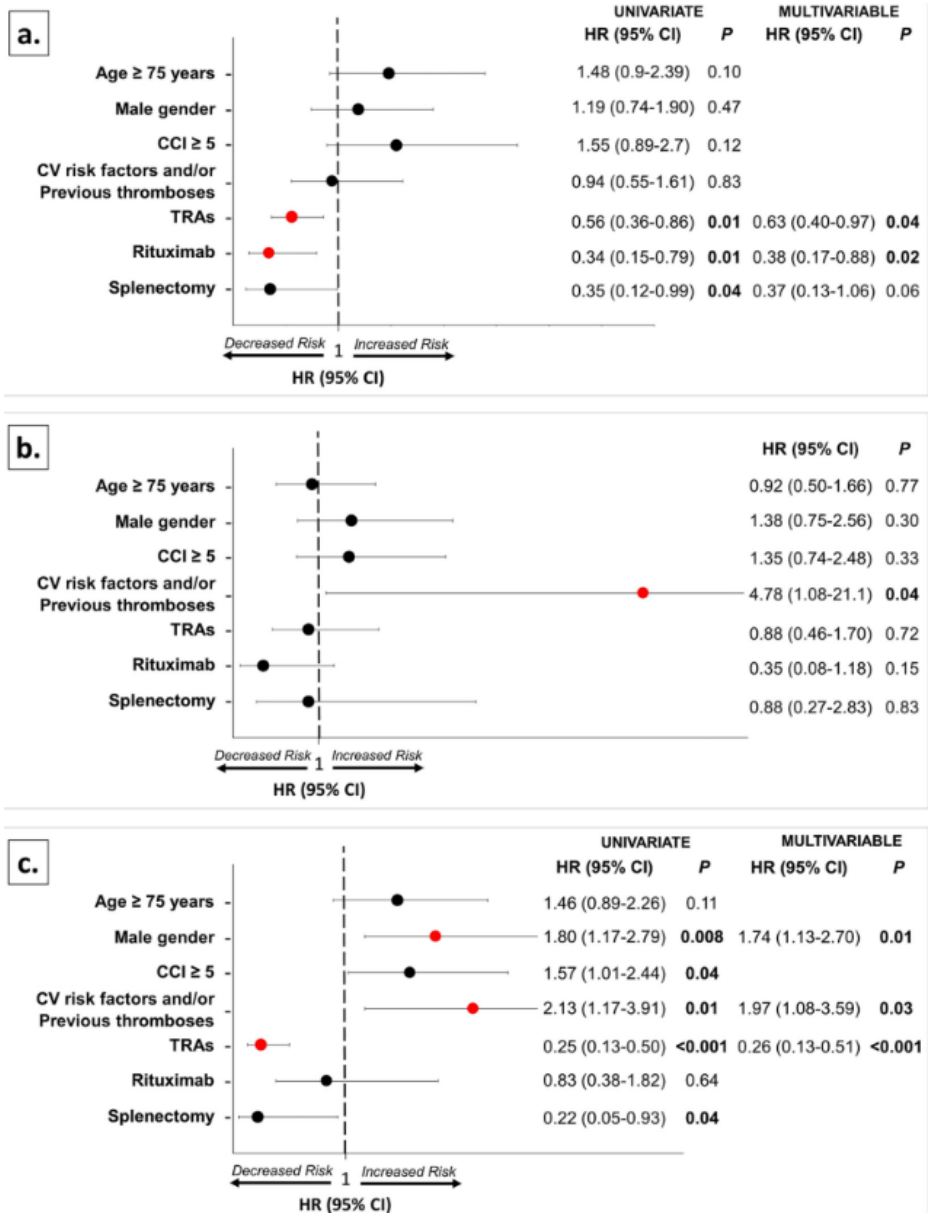
- Median age 71.1 years (age≥75: 42.8%); 237 (53.9%) haemorrages at diagnosis
- Thrombopoietin-receptor agonists (TRAs, 1.3% 1st line; 19.3% 2nd line; 4.4 % 3rd line)
- Overall response rates to first and second-line therapies were 83.8% and 84.5%, respectively, regardless of age and treatment type/dose.
- A total of 178 haemorrhages in 101 patients (grade ≥ 3: n. 52, 29.2%; intracranial in 6 patients), 49 thromboses in 43 patients (grade ≥ 3: n. 26, 53.1%) and 115 infections in 94 patients (grade ≥ 3:n. 23, 20%) were observed during follow-up.
- Incidence rates of complications per 100 patient-years: 4.5 (haemorrhages, grade ≥3: 1.7), 1.7 (thromboses, grade ≥ 3: 0.9), and 3.9 (infections, grade ≥ 3: 0.7).

https://www.sciencedirect.com/science/article/pii/S0049384819305201

F Palandri Thrombosis Research 185 (2020) 88–9590

Management of elderly patients with immune thrombocytopenia: Real-world evidence from 451 patients older than 60 years

- Thrombopoietin-receptor agonists may reduce risk of bleedings and infections in the elderly
- History of diabetes and thrombosis, but not TRAs use, increases thrombotic risk.



https://www.sciencedirect.com/science/article/pii/S0049384819305201

F Palandri Thrombosis Research 185 (2020) 88–9590

Real-world use of thrombopoietin receptor agonists in elderly patients with primary immune thrombocytopenia

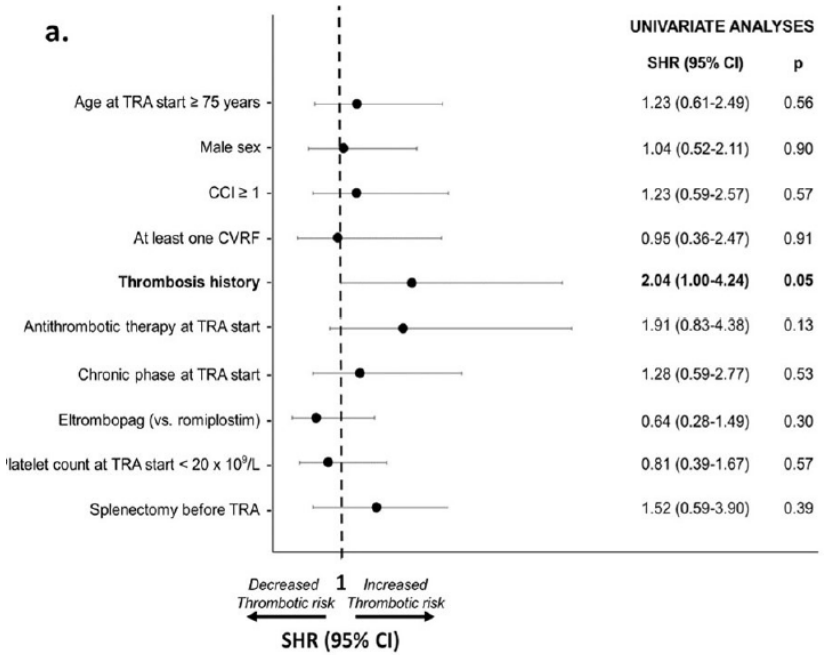
- A total of **384 ITP patients > 60 yrs treated with TRAs**
- After 3 months, 82.5% and 74.3% of eltrombopag and romiplostim-treated patients achieved a response, respectively (p=0.09);
- 66.7% maintained the response (median follow-up: 2.7 years).
- Eighty-five (22.2%) switched with 83.3% response
- 34 major thromboses (3 fatal) and 14 major hemorrhages (none fatal) in 18 and 10 patients, respectively, all associated with thrombosis history (SHR: 2.04, p=0.05) and platelet count <20x109/L at TRA start (SHR: 1.69, p=0.04), respectively.
- recurrent event in 15.6% of patients surviving thrombosis during persisting TRA treatment (incidence rate: 7.7 per 100 patient-years). All recurrences occurred in the absence of adequate antithrombotic secondary prophylaxis.
- Sixty-two (16.5%) responding patients discontinued TRA; 53 (13.8%) patients maintained SROT, which was associated with TRA discontinuation in complete response (p<0.001).
- Very old age (≥75, 41.1%) associated with more frequent TRAs start in persistent/acute phase but not with response or thrombotic/hemorrhagic risk.

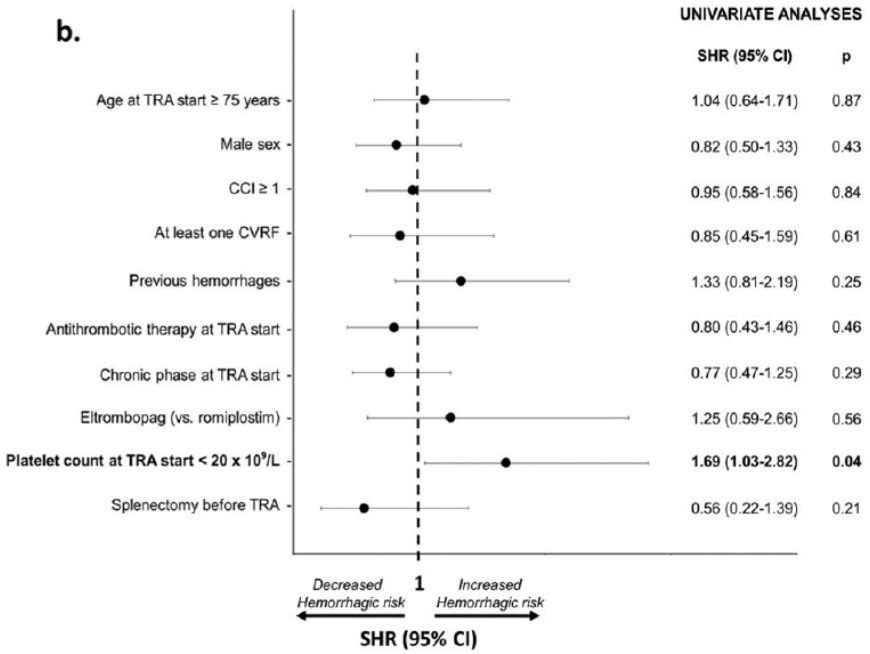
https://pubmed.ncbi.nlm.nih.gov/33889952/

F Palandri Blood APRIL 22, 2021

Real-world use of thrombopoietin receptor agonists in elderly patients with primary immune thrombocytopenia

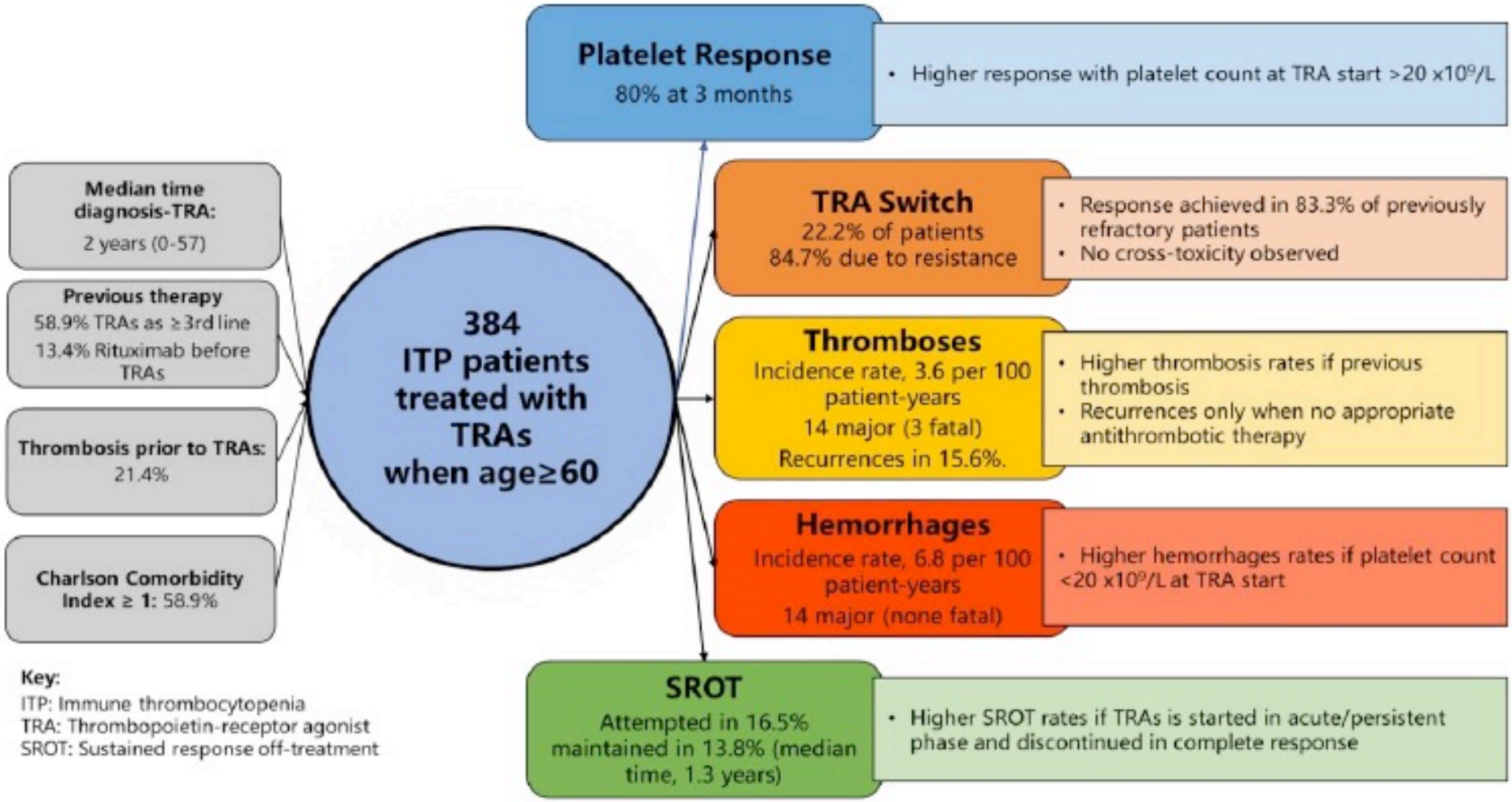
- Eltrombopag and romiplostim are effective in elderly ITP patients, with no fatal hemorrhages and 13.8% of sustained responses off-therapy
- Thrombosis history and absence of secondary antithrombotic prophylaxis are associated with thromboses and recurrent events during therapy





https://pubmed.ncbi.nlm.nih.gov/33889952/

F Palandri Blood APRIL 22, 2021


Median time diagnosis-TRA:
2 years (0-57)
Previous therapy
58.9% TRAs as ≥3rd line
13.4% Rituximab before TRAs
Thrombosis prior to TRAs:
21.4%
Charlson Comorbidity Index ≥ 1: 58.9%
384 ITP patients treated with TRAs when age≥60
Platelet Response
80% at 3 months
• Higher response with platelet count at TRA start >20 x10⁹/L
TRA Switch
22.2% of patients
84.7% due to resistance
• Response achieved in 83.3% of previously refractory patients
• No cross-toxicity observed
Thromboses
Incidence rate, 3.6 per 100 patient-years
14 major (3 fatal)
Recurrences in 15.6%.
• Higher thrombosis rates if previous thrombosis
• Recurrences only when no appropriate antithrombotic therapy
Hemorrhages
Incidence rate, 6.8 per 100 patient-years
14 major (none fatal)
• Higher hemorrhages rates if platelet count <20 x10⁹/L at TRA start
SROT
Attempted in 16.5%
maintained in 13.8% (median time, 1.3 years)
• Higher SROT rates if TRAs is started in acute/persistent phase and discontinued in complete response
Key:
ITP: Immune thrombocytopenia
TRA: Thrombopoietin-receptor agonist
SROT: Sustained response off-treatment

Come usare i TPO-Ra nei pazienti anziani?

Elderly ITP patients:
BALANCING THROMBOTIC, HEMORRHAGIC AND INFECTIOUS RISK

- Medical history
- Comorbidities
- Cardiovascular risk factors

- Adequate antithrombotic prophilaxis
- Prior therapies
- Platelet count

TPO-Ra e steroide c’è uno spazio….?

- **Per limitare le singole tossicità**
- In attesa che il nuovo farmaco faccia effetto
- Per massimizzare le risposte in urgenza
- In caso di improvvisa perdita di risposta al TPO

TPO-Ra prima linea …mai?

Controindicazioni assolute a Steroidi e/o HD-Ig ???