I TPO-MIMETICI NELLA REAL LIFE

Quando passare dallo steroide al TPO-mimetico

Dott.ssa Cristina Santoro
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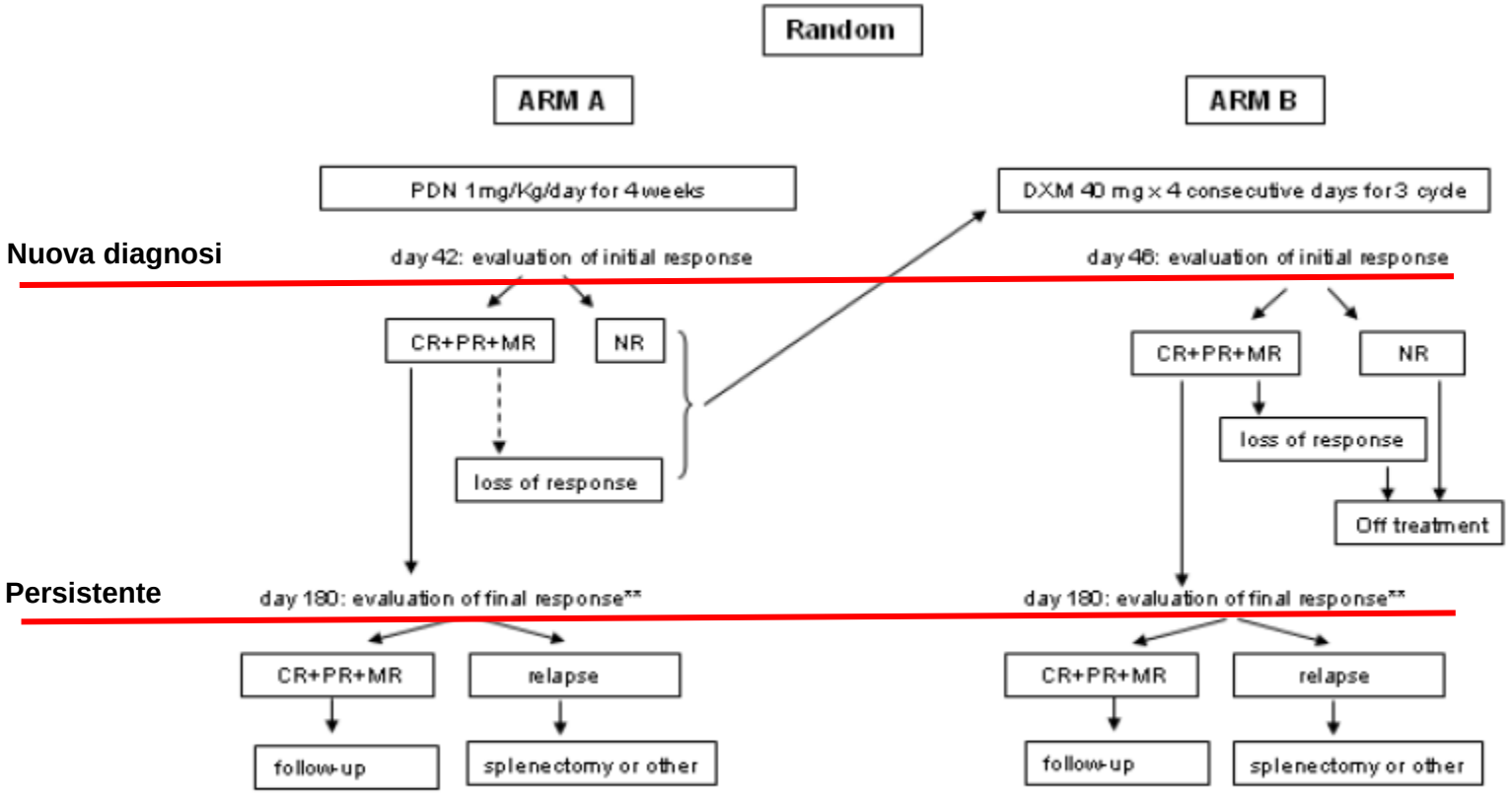
Randomized study for the treatment of primary Immune Thrombocytopenic Purpura (ITP) in newly diagnosed untreated adult patients.

Comparison of standard dose prednisone versus high-dose Dexamethasone.

GIMEMA Protocol ITP 0207

EudraCT number 2008-000417-30



** day 180: from the evaluation of initial response

I TPO-MIMETICI NELLA REAL LIFE

Dove inserire il TPO mimetico nella terapia della Piastrinopenia Immune Primitiva??

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Caso clinico 1

- Donna di 39 anni
- Settembre 2008: diagnosi di ITP (piastrine 2.000/mm^3; presenza di petecchie ed ecchimosi agli arti inferiore e superiori)
  Inizia terapia con Desametasone (DXM) 40 mg/die per 4 giorni per 3 cicli (1^a linea di terapia ⟹ Piastrine 79.000/mm^3
- Novembre 2008 (dopo 20 gg ultimo ciclo DXM): I RECIDIVA
  ⟹ Piastrine 8.000/mm^3
  Inizia Prednisone (PDN) 0,5 mg/kg/die per 4 settimane, che viene quindi ridotto modulandolo sulla base del numero delle piastrine e della sintomatologia emorragica
- Da luglio 2009 la paziente non risponde più alle dosi di mantenimento (PDN 5/10 mg a giorni alterni) Piastrine sempre <20.000/mm^3, in assenza di sintomatologia emorragica

SPLENECTOMIA

RITUXIMAB

La paziente, che è una straniera, ritorna nel suo paese di origine per un anno

- Luglio 2010: ritorna in visita e si decide di eseguire la splenectomia

Caso clinico 1

Settembre 2010: SPLENECTOMIA (2ª linea di terapia)

Dopo due boli di IGIV 1g/Kg (in preparazione dell'intervento) Piastrine 10.000/mm^3
Pertanto vengono trasfusi concentrati piastrinici: piastrine 150.000/mm^3;
si procede quindi a splenectomia.

Intervento senza complicanze.
Nei primi giorni post-operatori Piastrine: >400.000/mm^3

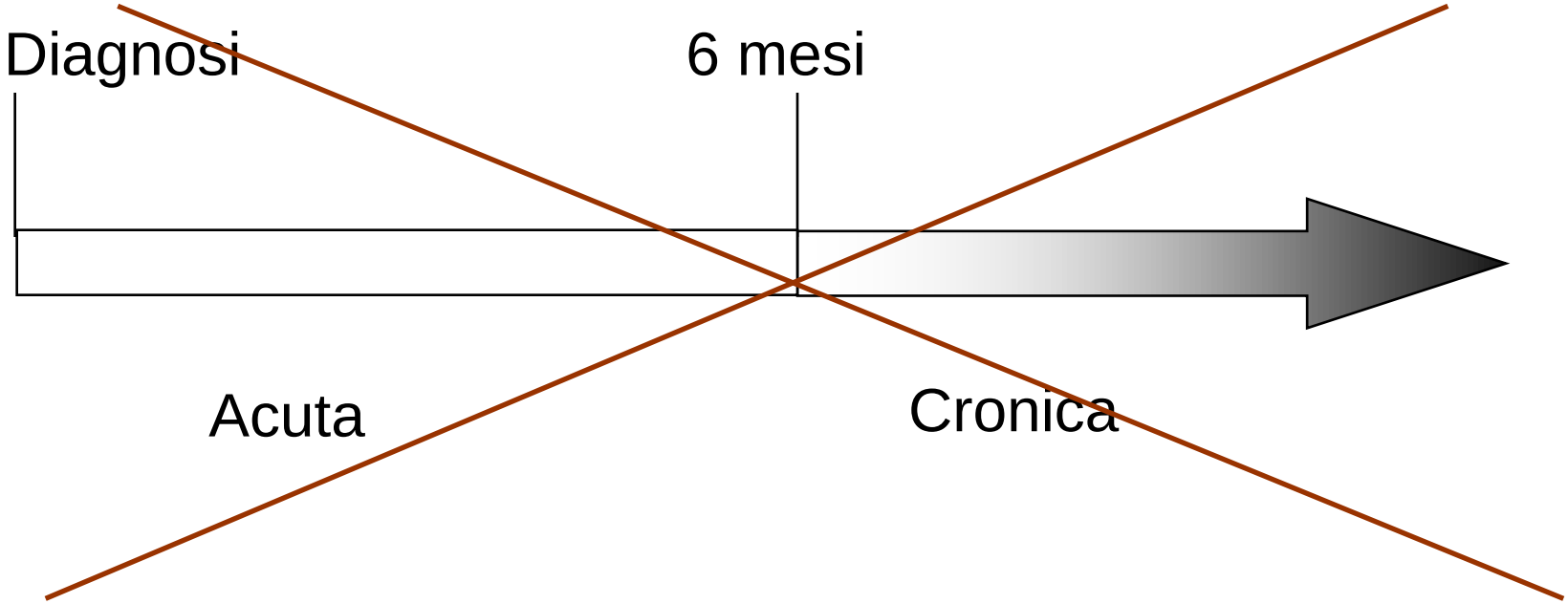
A 1 mese dall'intervento: piastrine 76.000/mm^3

Dicembre 2010: RECIDIVA POST SPLENECTOMIA
Piastrine < 10.000/mm^3; viene reinserito prednisone 10mg/die

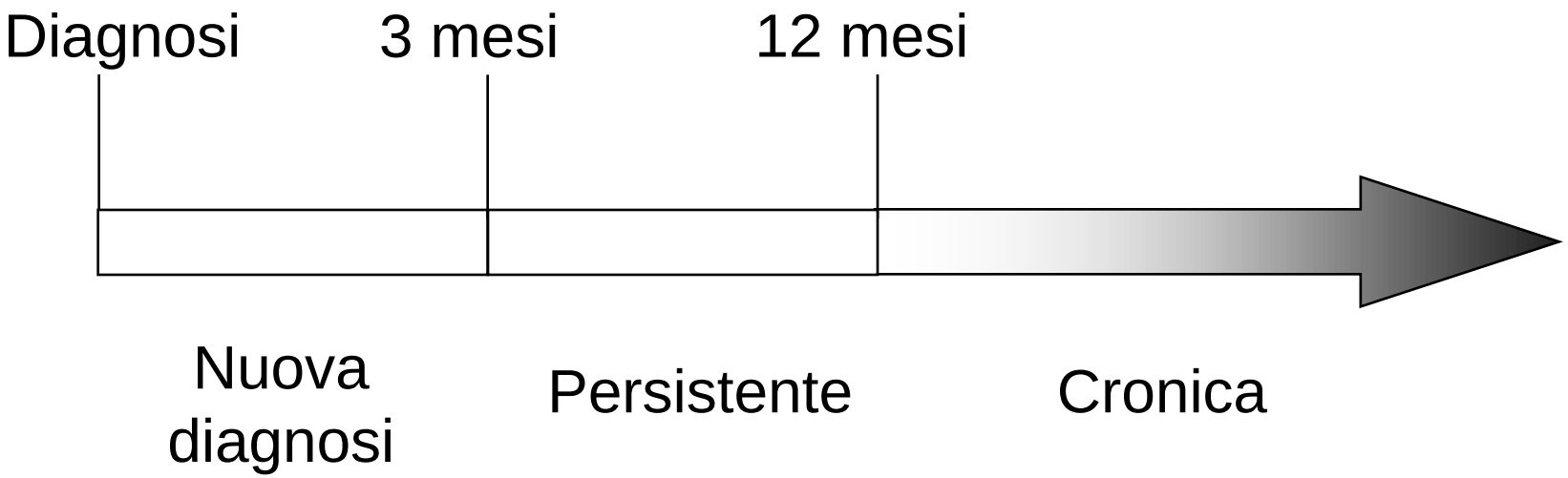
Gennaio 2011: inizio Eltrombopag (3ª linea di terapia)
Eltrombopag viene somministrato e modulato sul numero delle piastrine fino a giugno 2011, quando su un valore di piastrine pari a 700.000/mm^3 viene sospeso definitivamente

Aprile 2016
Ultimo follow-up con piastrine mai inferiori a 100.000/mm^3.

Fasi della ITP: vecchia terminologia



Fasi della ITP: nuova terminologia terminologia



Rodeghiero F et al, Blood 2009

Therapeutic goals

Phase of disease	Aim of treatment
Initial treatment	Obtain a safe platelet count (rapidly) to reduce bleeding or bleeding risk
Persistent disease	Defer/avoid toxic Immunosuppression or splenectomy
Chronic disease	Curative aim (?)
Refractory patients (after splenectomy)	Minimize the risk of bleeding; to increase the PLT count is not the main goal

blood
2010 115: 168-186
Prepublished online October 21, 2009;
doi:10.1182/blood-2009-06-225565

International consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan, Roberto Stasi, Adrian C. Newland, Victor S. Blanchette, Paula Bolton-Maggs, James B. Bussel, Beng H. Chong, Douglas B. Cines, Terry B. Gernsheimer, Bertrand Godeau, John Grainger, Ian Greer, Beverley J. Hunt, Paul A. Imbach, Gordon Lyons, Robert McMillan, Francesco Rodeghiero, Miguel A. Sanz, Michael Tarantino, Shirley Watson, Joan Young and David J. Kuter

Table 4. First-line treatment options for adult ITP patients

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Duration of sustained response
Corticosteroids				
Dexamethasone 40 mg daily for 4 d every 2-4 wk for 1-4 cycles	Up to 90% of patients respond initially	Several days to several weeks	Vary with length of administration: mood swings, weight gain, anger, anxiety, insomnia, Cushingoid faces, dorsal fat, diabetes, fluid retention, osteoporosis, skin changes including thinning, alopecia, hypertension, GI distress and ulcers, avascular necrosis, immunosuppression, psychosis, cataracts, opportunistic infections, adrenal insufficiency; hypertension, anxiety. Tolerability decreases with repeated dosing. Possibly lower rate of adverse events when used as short-term bolus therapy	As high as 50%-80% reported, the latter with 3-6 cycles (during 2-5 y of follow-up)
Methylprednisolone 30 mg/kg/d for 7 d	As high as 95%	4.7 d vs 8.4 d (high-dose methylprednisolone [HDMP] vs prednisone)		23% of patients have sustained platelet count (> 50 × 10^9/L) at 39 mo
Prednis(ol)one 0.5-2 mg/kg/d for 2-4 wk	70%-80% of patients respond initially	Several days to several weeks		Remains uncertain; estimated 10-y disease-free survival 13%-15%
IV anti-D				
50-75 μg/kg	Initial response rate similar to IVIg (dose dependent)	4-5 d	Common: hemolytic anemia (dose-limiting toxicity), fever/chills Rare: intravascular hemolysis, disseminated intravascular coagulation, renal failure, rare death	Typically last 3-4 wk but may persist for months in some patients
IVIg*				
0.4 g/kg/d for 5 d or infusions of 1 g/kg/d for 1-2 d	Up to 80% of patients respond initially; half achieve normal platelet counts	Rapid; many respond in 24 h; typically 2-4 d	Headaches common: often moderate but sometimes severe Transient neutropenia, renal insufficiency, aseptic meningitis, thrombosis, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia IVIg preparations may contain small quantities of IgA, which occasionally causes anaphylactoid reactions in patients with IgA deficiency; in these cases use IgA-depleted IVIg	Usually transient; platelet counts returning to pretreatment levels 2-4 wk after treatment; persists for months in a few patients

Full details regarding the studies found in the literature search are available in supplemental Document 3.
*IVIg may be discontinued after 1 to 2 days if adequate response is seen.

blood

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Table 3. Therapies for the treatment of ITP

Clinical situation	Therapy option
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 Vinca alkaloids
Treatment for patients failing first- and second-line therapies	**Category A: treatment options with sufficient data** TPO receptor agonists **Category B: treatment options with minimal data and considered to have potential for considerable toxicity** Campath-1H Combination of first- and second-line therapies Combination chemotherapy HSCT

Treatment options for ITP are listed in alphabetical order and thus do not imply a preferred treatment option.

HSCT indicates hematopoietic stem cell transplantation; TPO, thrombopoietin; and IVIg, intravenous immunoglobulin.

L'ICS riporta una lista di terapie di seconda linea, elencate in ordine alfabetico, perché ritenute insufficienti le evidenze per elencare tali trattamenti secondo un ordine di efficacia (a parte i TPO mimetici che sono stati studiati attraverso trials randomizzati).

The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia

*Cindy Neunert,[1] *Wendy Lim,[2] Mark Crowther,[3] Alan Cohen,[4] Lawrence Solberg Jr,[5] and Mark A. Crowther[2]

[1]University of Texas, Southwestern Medical Center, Dallas, TX; [2]McMaster University, Hamilton, ON; [3]Worcestershire Royal Hospital, Worcester, United Kingdom; [4]Children's Hospital of Philadelphia, Philadelphia, PA; and [5]Mayo Clinic, Jacksonville, FL

Trattamento di I linea

4.3.A. We suggest:

- Longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIg as first-line treatment (grade 2B).
- IVIg be used with corticosteroids when a more rapid increase in platelet count is required (grade 2B).
- Either IVIg or anti-D (in appropriate patients) be used as a first-line treatment if corticosteroids are contraindicated (grade 2C).
- If IVIg is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary (grade 2B).

Il documento dell'ASH è più simile alle tradizionali Linee Guida dal momento che offre un livello di evidenza più dettagliato, e il grado di forza dell'evidenza viene utilizzato per raccomandare o suggerire differenti opzioni di gestione della patologia

Trattamento di II linea

4.4.A. We recommend:

- Splenectomy for patients who have failed corticosteroid therapy (grade 1B).
- Thrombopoietin receptor agonists for patients at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy (grade 1B).

4.4.B. We suggest:

- Thrombopoietin receptor agonists may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not had splenectomy (grade 2C).
- Rituximab may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy (grade 2C).

ITP persistenti

- None of the available GL specifically addresses patients with persistent ITP (as no data are available in literature apart from anecdotal evidence in sparse cases)

- In both ICR and ASH-2011 GL, patients not responding to first-line treatments (corticosteroids, IVIg, anti-D) are lumped together in a single heterogeneous category irrespective of the different phases of disease (newly diagnosed, persistent or chronic ITP)

- This precludes separate considerations for patients failing initial corticosteroids but still with a short disorder duration – and thus at a more favorable prognosis – from those with a more advanced disease and thus probably already exposed to more lines of medical treatments.

- Both GL just suggest that, if splenectomy is deemed necessary, surgery should be deferred for at least 6 months (ICR) or 12 months (ASH-2011) from diagnosis.

- Considering that 50 to 80% of initially treated patients will relapse and require further treatment after failing initial corticosteroids, the most appropriate treatment of patients with persistent ITP represents an area of major clinical interest burdened by unacceptable uncertainty.

Rodeghiero F, Ruggeri M. Presse Med. 2014

ITP persistenti

• A general rule is to spare these patients treatments with long-term adverse effects such as prolonged use of corticosteroids, immunosuppressive drugs or chemotherapy

• Sometimes, on demand therapy is the only treatment used at the time of or in anticipation of high risk bleeding situations. In other cases, the lowest effective dose of corticosteroids is maintained for weeks or months.

• Dapsone, an inexpensive drug with a well-established safety profile, could also prove useful in this setting. Danazol administration could also be a useful alternative to spare corticosteroids until a decision on splenectomy has, eventually, been taken

However, with the advent of TPO-RA which have a response rate in 60–70% of cases and are apparently devoid of major short-or medium-term toxicity, one could consider to treat with these agents patients at risk of bleeding while in persistent phase as a bridge to splenectomy, thus sparing them more toxic agents or more demanding treatments like in-hospital administration of IVIg.

This approach will allow to safely manage patients while waiting for a possible remission, either spontaneous or facilitated by these agents as recently suggested, or to take a definite orientation towards a treatment with curative potential like splenectomy or rituximab. This is clearly an area that deserves further studies.

Rodeghiero F, Ruggeri M. Presse Med. 2014

Precedenti indicazioni EMA

I farmaci TPO-RAs (thrombopoietin receptor agonists), ROMIPLOSTIM ed ELTROMBOPAG sono stati approvati da EMA* per il trattamento di pazienti adulti affetti da pITP cronica che siano refrattari o recidivati dopo la splenectomia, o nei quali la splenectomia sia controindicata.

*romiplostim: novembre 2009; eltrombopag: marzo 2010

REVOLADE Eltrombopag: indicazioni registrate EMA

INDICAZIONE

Revolade è indicato in pazienti di età superiore ad un anno affetti da porpora trombocitopenica autoimmune (idiopatica) cronica (PTI) che sono refrattari ad altri trattamenti (ad esempio corticosteroidi, immunoglobuline).

APPROVAZIONE

- *Febbraio 2016 (Cambio ITP)*
- *Aprile 2016 (ITP pediatrica)*

N-Plate Romiplostim: indicazione registrata EMA

N-Plate è indicato in pazienti adulti affetti da piastrinopenia immune primitiva (pITP) cronica, resistenti ad altri trattamenti (ad esempio corticosteroidi, immunoglobuline).

APPROVAZIONE

- *Aprile 2016*

Exposure to non-corticosteroid treatments in adult primary immune thrombocytopenia before the chronic phase in the era of thrombopoietin receptor agonists in France. A nationwide population-based study

•Study aim: to describe the exposure to non-corticosteroid treatments in adult primary ITP patients **before the chronic phase** at a nationwide level.

•The study population: 443 patients.

•Non-corticosteroid treatments used in more than 10% of the patients at any time before the chronic phase: rituximab (57.8%), splenectomy (22.1%), TPO-RAs (16.8%), repeated IVIg courses (15.0%), danazol (14.4%), dapsone (10.8%).

•TPO-RAs were used as first-line non-corticosteroid treatment **in only 6.3% of the patients**, so less frequently than rituximab, splenectomy, IVIgs, danazol and dapsone.

•However, 11.8% of older patients have been exposed to TPO-RAs as first-line non-corticosteroid treatment compared with 3.5% of younger patients ($p = 0.0006$).

•Our study points that TPO-RAs were not used in most patients as first-line non-steroid treatment, suggesting a use in accordance with their labeling.

•* This study could not assess whether all non-steroid treatments were prescribed after a corticosteroid exposure, and whether it was because of corticosteroid-dependency or corticosteroid-resistance.

Moulis G et al. Autoimmun Rev 2015

A United Kingdom Immune Thrombocytopenia (ITP) Forum review of practice: thrombopoietin receptor agonists

A 12-question survey was designed to assess several aspects of prescribing practice for TPO-RA in UK.

14/20 (70%) adult clinical centres responded by November 2015

Most respondents positioned TPO-RAs ahead of splenectomy, but usually after at least one alternative second line agent. Many cited that individual patient factors (including preference) or local funding arrangements influenced this decision.

NICE recommendations reflected the EMA marketing authorisation for TPO-RA at the time (TPO-RA use in (i) patients with refractory chronic ITP post-splenectomy or (ii) when splenectomy is contra-indicated, in those refractory to standard and rescue therapies or with severe disease needing frequent rescue therapies)

However TPO-RAs remain the only licensed, best studied and most efficacious second line medical therapy
The EMA authorization was revised in December 2015 to 'adult chronic immune (idiopathic)
ITP patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)' and for eltrombopag in January 2016 to 'patients age 1 year and above who are refractory to other treatments e.g. corticosteroids, immunoglobulins'.

Table I. Thrombopoietin receptor antagonist questionnaire.

Question	Responses
1) When would you start TPO-RAs?	In addition to NICE indications, all 14 respondents would consider TPO-RAs before splenectomy in some situations. The majority (8/14) would use TPO-RAs after failure of one steroid-sparing agent (mycophenolate or rituximab). Two after failure of two steroid-sparing agents (oral immunosuppression then rituximab). Three presented TPO-RAs as a second line option to patients (vs. mycophenolate, rituximab or splenectomy). One respondent would follow NICE guidance but consider second line use in bleeding patients failing steroids and IVIg.

Based on available evidence, we draw the following conclusions:

1 Although decisions must still be individualised, TPO-RAs should be considered in patients who have failed first line therapy.

Thachil A et al. Br J Haematol 2016

Have splenectomy rate and main outcomes of ITP changed after the introduction of new treatments? A monocentric study in the outpatient setting during 35 years

Francesca Palandri,* Nicola Polverelli, Daria Sollazzo, Marco Romano, Lucia Catani, Michele Cavo, and Nicola Vianelli

The description of outpatients is extremely important to understand and analyze the changes in therapeutic strategies over time and their efficacy and safety rates.

Here, we hypothesized that new drugs (RTX and TPO-R agonists) may have induced a decreased use of splenectomy. In addition, we investigated whether and to what extent new agents had modified outcomes rates.

397 pts I linea
219 pts II linea
96 pts III linea

Palandri F et al. Am J Hematol 2016

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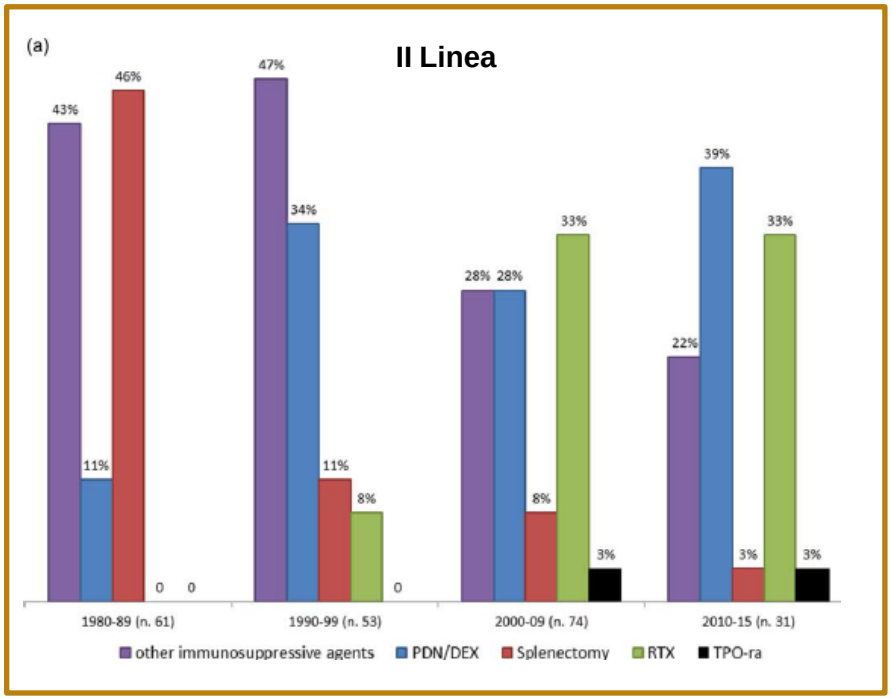

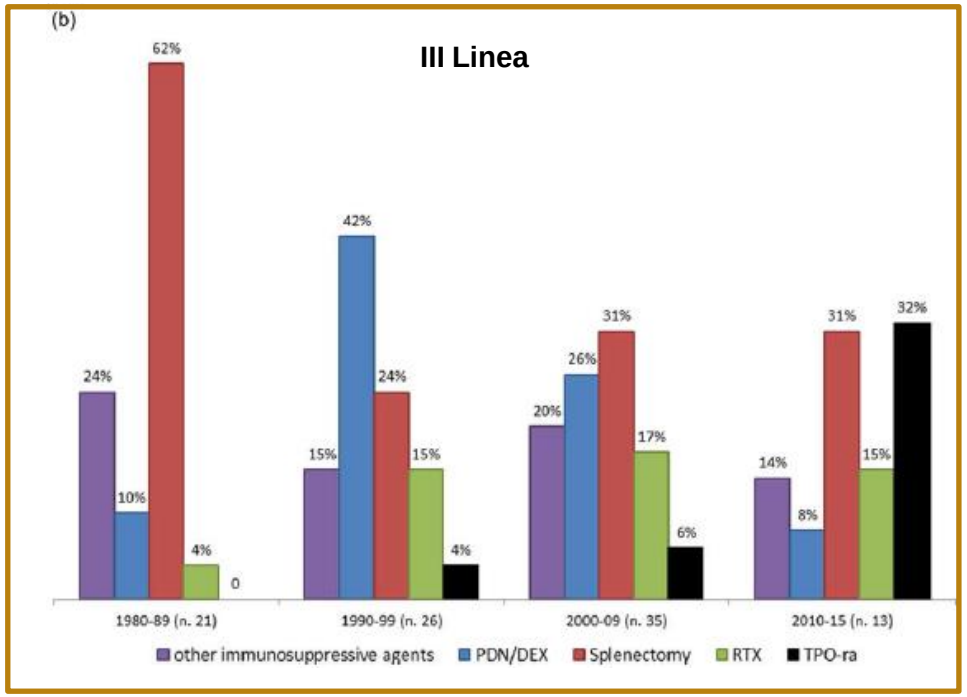

Figure 1. Treatment strategies in second-line (a) and third-line (b) according to the years of diagnosis. Percentages refers to the number of patients submitted to that specific treatment second-line out of the overall number of patients treated second-line (a) or to the number of patients submitted to that specific treatment third-line out of the overall number of patients treated third-line (b) in every decade. Other immunosuppressant agents include: azathioprine, cyclosporine, vincristine and cyclophosphamide; PDN, prednis(ol)one; DEX, dexamethasone; RTX, rituximab; TPO-ra, trombopoietin-receptor agonists.

Palandri F et al. Am J Hematol 2016

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•From the 2000s onwards, TPO-R agonists eltrombopag and romiplostim have emerged as the third-line treatment of choice, partially replacing a prolonged use of immunosuppressive drugs.

•More than 15% of patients received TPO-R agonists during the first 12 months from ITP diagnosis.

•In some cases, TPO-R agonists were reserved to older patients that were not eligible to surgery and/or RTX administration.

•However, from the 2010s onwards TPO-R agonists were also used in younger patients with persistent ITP, with the purpose to discontinue the drug whenever a stable response was obtained, and/or as a bridge to splenectomy.

Palandri F et al. Am J Hematol 2016

Thrombopoietin receptor agonists for preparing adult patients with immune thrombocytopenia to splenectomy: results of a retrospective, observational GIMEMA study

•31 adult patients, median age 50 years, with corticosteroids and/or IVIG refractory persistent and chronic ITP
•Treated with TPO-RAs (romiplostim 24; eltrombopag 7) with the aim to increase platelet count and allow a safer execution of splenectomy.

•24/31 patients (77%) responded to the use of TPO-RAs with a median platelet count that increased from 11 x 10^9/L before starting TPO-RAs to 114 x 10^9/L pre-splenectomy, but a concomitant treatment with corticosteroids and/or IVIG was required in 19 patients.

•29 patients underwent splenectomy while two patients who responded to TPO-RAs subsequently refused surgery.

•Post-splenectomy complications:
- •Two Grade 3 thrombotic events (1 portal vein thrombosis in the patient with previous history of HCV hepatitis and 1 pulmonary embolism), with a platelet count at the time of thrombosis of 260 and 167 x 10^9/L,
- • One Grade 3 infectious event.

TPO-RAs may represent a therapeutic option to improve platelet count and reduce the risk of peri operative complications in ITP candidates to splenectomy.
An increased risk of post-splenectomy thromboembolic events cannot be ruled out and thromboprophylaxis with low-molecular weight heparin is generally recommended.

Zaja F et al. Am J Hematol 2016

Risposta sostenuta off-treatment dopo TPO-RAs

Of course, the finding that some patients treated with TPO-ra may achieve a response or complete response of variable duration after their suspension, although still limited to a thin percentage of patients, is encouraging and may favor their use before splenectomy.

However, ‘‘spontaneous’’ improvements of ITP are described even after 2 o 3 years from diagnosis in non splenectomized patients.

Rodeghiero F, Ruggeri M. Presse Med. 2014

An unexpected finding has been that up to a third of patients responding to TPO-RA can be weaned off treatment and still maintain their response. All respondents would taper TPO-RA after a period with stable normal platelet counts.

Thachil A et al. Br J Haematol 2016

How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment

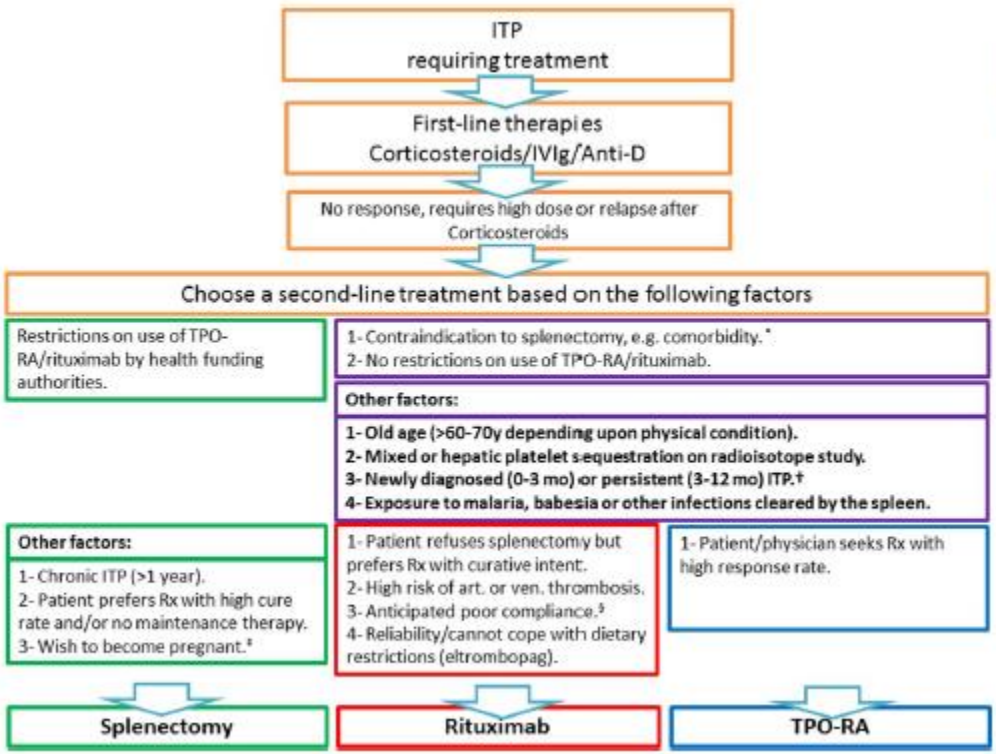

Figure 2. Suggested treatment algorithm for ITP. *These are overall factors that go for or against splenectomy without distinguishing between TPO-RA and rituximab. †Based on recommendations to defer splenectomy for 1 year, if possible. ‡Alternative option is rituximab, and wait for 12 months before conception. §Anticipated poor compliance is also applicable to splenectomy, although post-splenectomy management (eg, repeat vaccination, management of febrile illness, and follow-up regarding platelet count) would probably also be at risk.

The last decade has seen the introduction of new exciting suitable second-line medical approaches to manage adults with ITP. Each approach has unique benefits, limitations, and risks, and none has been subjected to head-to-head comparisons.

Therefore, **optimal treatment will continue to involve a personalized approach to therapy** that combines the art of medicine with the science through close collaboration between patients and healthcare providers or the foreseeable future.

Ghanima W et al, Blood 2012

Terapia personalizzata

Moreover, the treatment should be tailored to the individual patient taking into account the presence and severity of bleeding, the rapidity of response and the expected side effects and costs.

Rodeghiero F, Ruggeri M. Presse Med. 2014

Caso clinico 2

Donna di 50 anni
29 Marzo 2013: diagnosi di ITP piastrine 2.000/mm^3; presenza di ematuria e gengivorragia.
29-3-2013: viene ricoverata e inizia terapia con prednisone 1 mg/kg/die + Ig 1 g/kg

Data	Piastrine	Sintomatologia emorragica	Trattamento
31-3-2013	6000/mm^3	Presente	PDN 1 mg/kg/die
1-4-2013	7000/mm^3	Presente	Aumenta PDN 2 mg/kg/die
3-4-2013	8000/mm^3	Presente	PDN 2 mg/kg/die + trasfusione di plts
8-4-2013	5000/mm^3	Presente	PDN 2 mg/kg/die + trasfusione di plts
16-4-2013	11000/mm^3	Ridotta	PDN 2 mg/kg/die. Inizia Romiplostim 2 mcg/kg
23-4-2013	2000/mm^3	Assente	PDN 2 mg/kg/die Incrementa Romiplostim 4 mcg/kg
30-4-2013	10000/mm^3	Assente	PDN 2 mg/kg/die Incrementa Romiplostim 6 mcg/kg
7-5-2013	63000/mm^3	Assente	PDN 2 mg/kg/die. Esegue Romiplostim 6 mcg/kg
13-5-2013	100000/mm^3	Assente	PDN 2 mg/kg/die. Esegue Romiplostim 6 mcg/kg
20-5-2013	135000/mm^3	Assente	PDN 2 mg/kg/die. Esegue Romiplostim 6 mcg/kg
27-5-2013	550000/mm^3	Assente	PDN 2 mg/kg/die. Sospende Romiplostim

Dal 27-5-2013 scala il cortisone fino a sospenderlo il 5-7-2013.
Non più eseguito Romiplostim.Ultimo follow-up: novembre 2016: Plts 248000/mm^3. Mai recidive

Conclusioni

Lo scenario clinico di utilizzo dei TPO-RA sta rapidamente cambiando, molto più velocemente rispetto alle Linee Guida ufficiali

Le nuove indicazioni EMA hanno colto e accolto tali nuovi scenari di utilizzo

Si renderebbe necessaria una revisione di tali Linee Guida alla luce delle nuove pratiche cliniche di utilizzo, e delle nuove conoscenze nell'uso dei TPO-RA.

Al centro delle decisioni c'è comunque il paziente su cui deve essere ritagliata la migliore terapia possibile, per ottenere il migliore risultato possibile con la minore tossicità: terapia personalizzata.