Prise en charge du PTI en 2022

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First line treatments

- **Steroids**
  - Prednisone, 1 mg/kg/j, short course+++
  - **Dexamethasone, 40mg/j pdt 4 j**
  - High dose methylprednisolone
- **IVIg**
- **Platelet transfusion**

Bleeding score is useful!

High-dose dexamethasone compared with prednisone for previously untreated primary ITP: a systematic review and meta-analysis

Similar long-term response

More rapid response

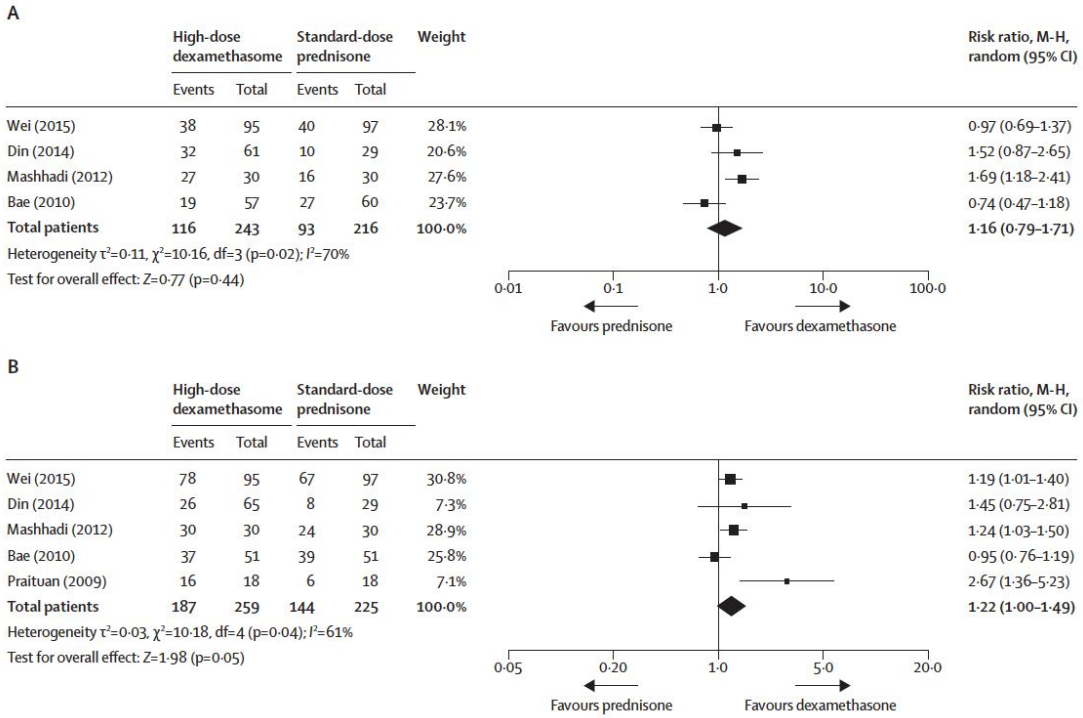


Figure 2: Platelet count responses in adults after treatment with high-dose dexamethasone versus standard-dose prednisone
(A) Overall response at 6 months or longer after treatment. **(B) Overall response within 14 days of treatment.**

Mithoowani S, et al. Lancet Haematol 2016;3:e489–e496.

IgIV et PTI

- **ATTENTION PENURIE !**
- Uniquement pour les malades qui en ont besoin!
- A la bonne posologie!
  - 1 g/kg J1 uniquement et 1 g/kg à J3 si pas de réponse
  - 1 g/kg J1 et J2 **uniquement si urgence vitale**
- Attention aux effets secondaires

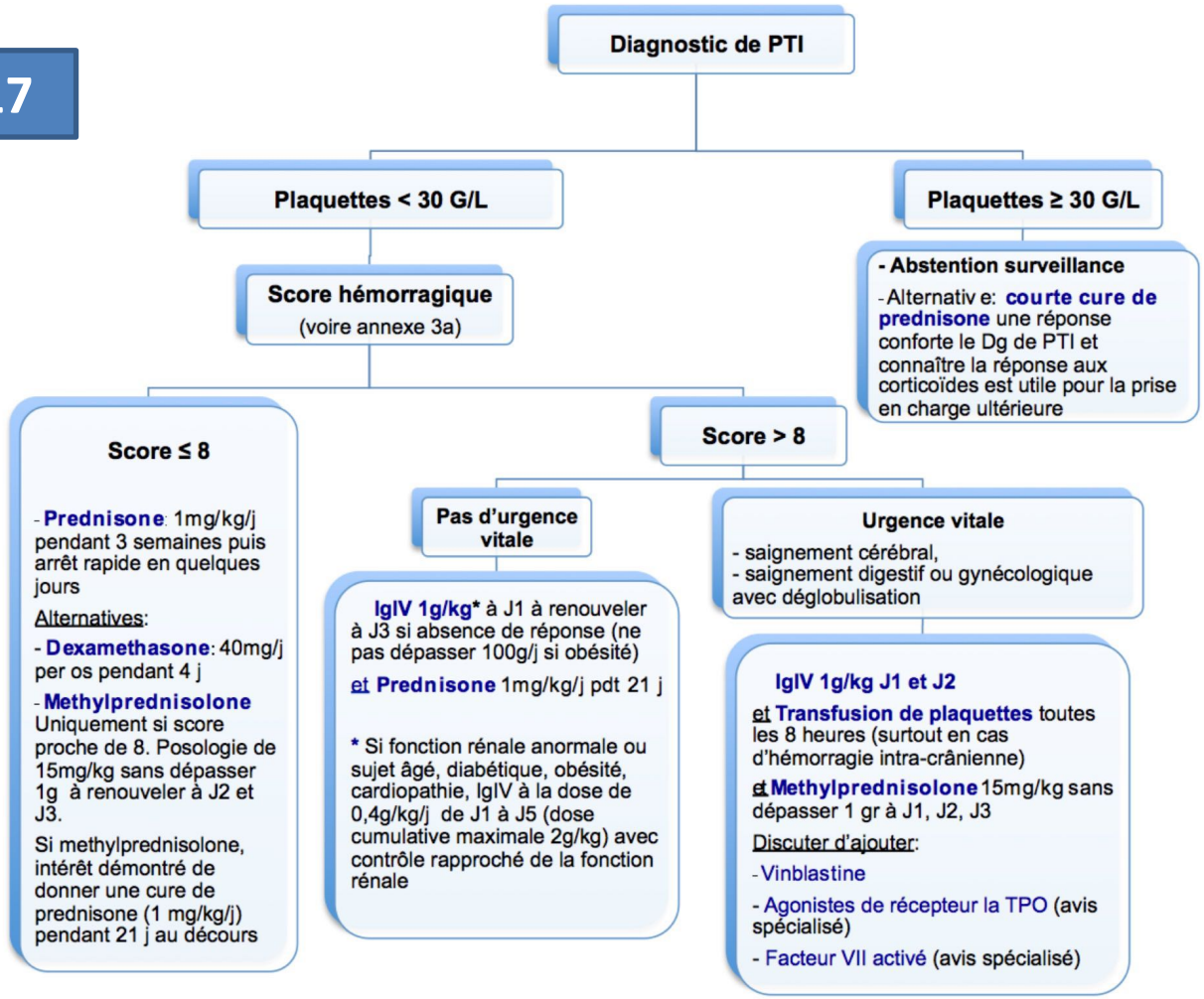
Annexe 3a. Score hémorragique utilisable chez l'adulte pour guider la prescription d'immunoglobulines intraveineuses*

(d'après Khellaf et al, Haematologica 2005; 90 : 829-32).

Age		**Saignement gastrointestinal**	
Age > 65 ans	2	Saignement digestif sans anémie	4
Age > 75 ans	5	Saignement digestif avec anémie (perte de plus de 2 g d'hémoglobine) et/ou choc	15
Saignement cutané		**Saignement urinaire**	
Purpura pétéchial localisé (membres)	1	Hématurie macroscopique sans anémie	4
Purpura ecchymotique	2	Hématurie macroscopique avec anémie aiguë	10
Purpura pétéchial avec localisations multiples	3	**Saignement du système nerveux central (SNC)**	
Purpura pétéchial généralisé	3	Saignement du SNC ou saignement avec mise en jeu du pronostic vital	15
Purpura ecchymotique généralisé	4		
Saignements muqueux			
Epistaxis unilatérale	2		
Epistaxis bilatérale	3		
Bulles hémorragiques spontanées ou gingivorragies spontanées	5		

* Pour chaque rubrique, seul le score le plus élevé est pris en compte. Un traitement par IgIV associées aux corticoïdes est proposé pour les patients ayant un score hémorragique supérieur à 8. En l'absence de contre-indication, les corticoïdes sont proposés en monothérapie en première intention en cas de score hémorragique ≤ 8.

PNDS 2017

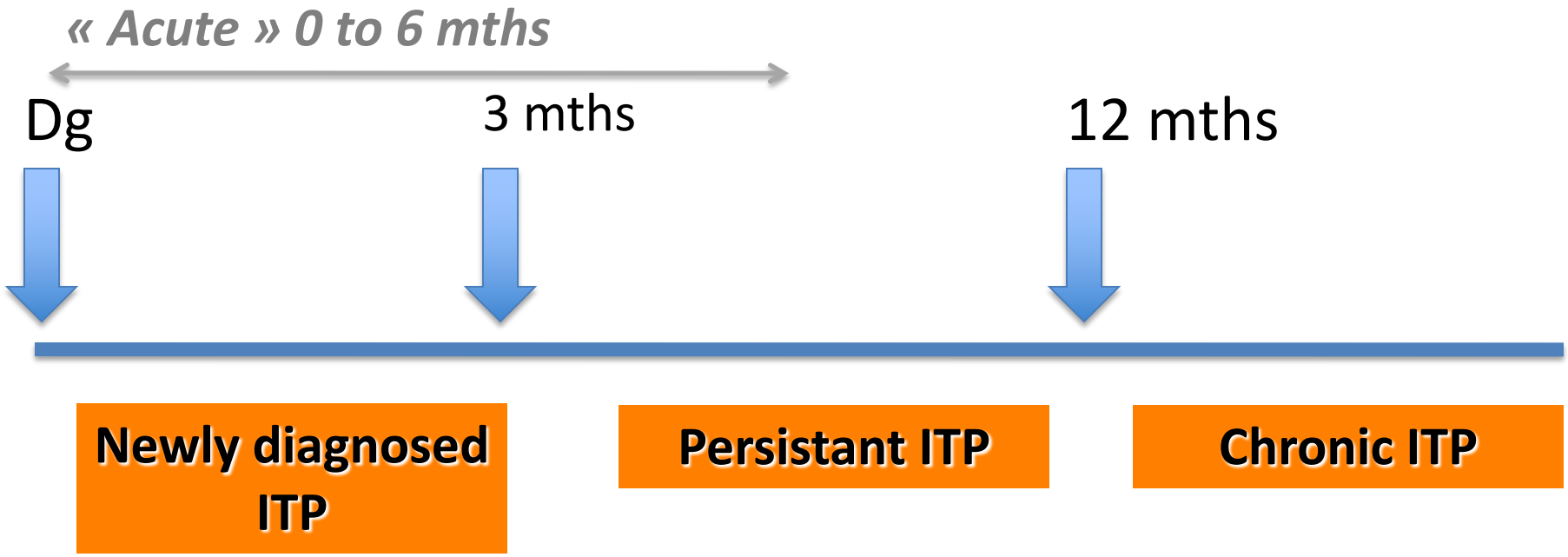

Diagnostic de PTI
Plaquettes < 30 G/L
Plaquettes ≥ 30 G/L
- Abstention surveillance
- Alternative: courte cure de prednisone une réponse conforte le Dg de PTI et connaître la réponse aux corticoïdes est utile pour la prise en charge ultérieure
Score hémorragique
(voire annexe 3a)
Score ≤ 8
- Prednisone: 1mg/kg/j pendant 3 semaines puis arrêt rapide en quelques jours
Alternatives:
- Dexamethasone: 40mg/j per os pendant 4 j
- Methylprednisolone Uniquement si score proche de 8. Posologie de 15mg/kg sans dépasser 1g à renouveler à J2 et J3.
Si methylprednisolone, intérêt démontré de donner une cure de prednisone (1 mg/kg/j) pendant 21 j au décours
Score > 8
Pas d'urgence vitale
IgIV 1g/kg* à J1 à renouveler à J3 si absence de réponse (ne pas dépasser 100g/j si obésité)
et Prednisone 1mg/kg/j pdt 21 j
* Si fonction rénale anormale ou sujet âgé, diabétique, obésité, cardiopathie, IgIV à la dose de 0,4g/kg/j de J1 à J5 (dose cumulative maximale 2g/kg) avec contrôle rapproché de la fonction rénale
Urgence vitale
- saignement cérébral,
- saignement digestif ou gynécologique avec déglobulisation
IgIV 1g/kg J1 et J2
et Transfusion de plaquettes toutes les 8 heures (surtout en cas d'hémorragie intra-crânienne)
et Methylprednisolone 15mg/kg sans dépasser 1 gr à J1, J2, J3
Discuter d'ajouter:
- Vinblastine
- Agonistes de récepteur la TPO (avis spécialisé)
- Facteur VII activé (avis spécialisé)

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

F Rodeghiero et al

BLOOD, 12 MARCH 2009; 113, 2386-93

ITP duration



Second line treatments

- Eradication of H Pylori
- **Dapsone –** Danatrol
- **Rituximab**
- **TPO-Ras**
- **Immunosuppressants**
- **Splenectomy**
- **Anti Syk (fostamatinib)***

* Réservé aux échecs des traitements de seconde ligne

Dapsone and ITP

PROS

- 30 to 50% of response rate
- Not expensive
- Well tolerated

CONS

- Cutaneous hypersensitivity
- CI G6PD deficiency
- Relapse if stopping
- Not effective in splenectomized patients
- Absence of license

Rodrigo et al, J Thrombos Haemost 2013; 11:1946-53

Rituximab: efficacy for ITP

- **Arnold *et al*.[1] systematic review (2007)**
  - 313 patients across 19 studies
  - **ORR*: 62.5%**
  - Median time to response: 5.5 weeks (range: 2–18)
  - Median response duration: 10.5 months (range: 3–20)

- **Auger *et al*.[2] meta-analysis (2012)**
  - 368 non-splenectomised patients across 19 studies
  - **ORR*: 57%**
  - CR†: 41.5%

*Platelet count >50 x 10^9/L; †differed between studies (platelet count >100 x 10^9/L or >150 x 10^9/L)
CR, complete response; ORR, overall response rate.

1. Arnold D, *et al. Ann Intern Med* 2007;146:25–33;
2. Auger S, *et al. Br J Haematol* 2012;158:386–9.

- **Anti CD20** (rituximab, veltuzumab): **PRO**
  - Good short term-response (50-60%)
  - Relatively not expensive
  - Simple to administer (fixed dose 1g D1 - D14)
  - Good safety with acceptable risk of infection
  - **But modest long-term response (20-25%)**

- **Outlook**:
- **How can we obtain better long-term results?**
  - **Associate RTX with other Tt?**
  - **Maintenance treatment?**

Rituximab and ITP: modest long term response

Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients
Khellaf M, *et al. Blood* 2014;124:3228–36

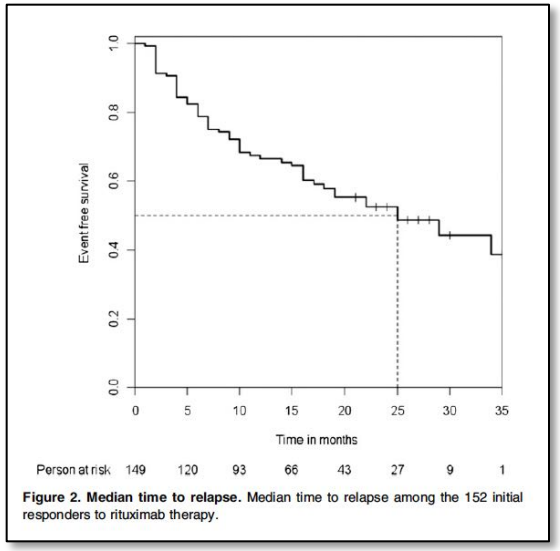


Figure 2. Median time to relapse. Median time to relapse among the 152 initial responders to rituximab therapy.

Median time to relapse: 25 months

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;385:1653–61

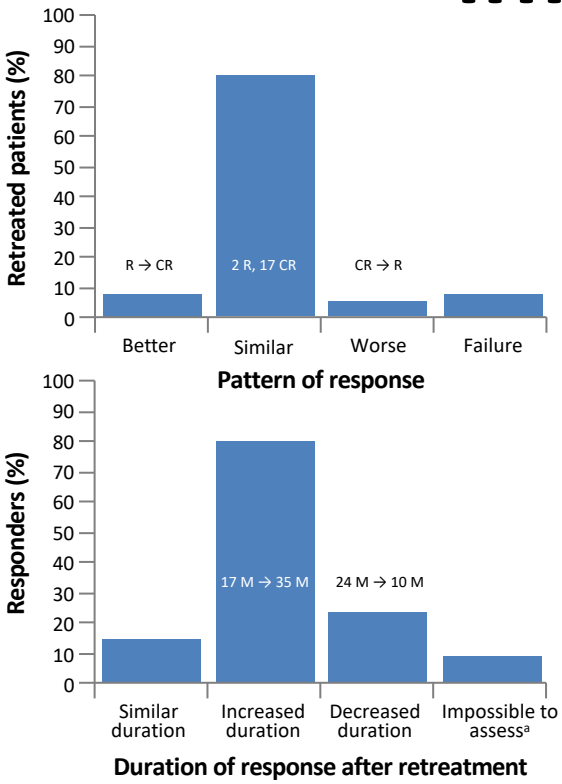
	RTX (n=55)	Placebo (n=54)	P
Median duration of complete response (weeks)	76 (32–NR)	49 (20–95)	0.19

NR, not reached.

Rituximab and ITP
How can we obtain better long-term results?

- Better selection of the patients?
  - Predictive factors of sustained response?
- Repeated infusions ?
- Use other CD20 ?
- Associate rituximab with dexamethasone ?

Rituximab and ITP: repeated infusions



In cases of response to the first course, **92%** of responses were observed after the second course

In **54%** of cases, the duration of response to the second course was increased

[a] In 2 patients, a more prolonged follow-up was required to be able to evaluate the duration of the response to retreatment.

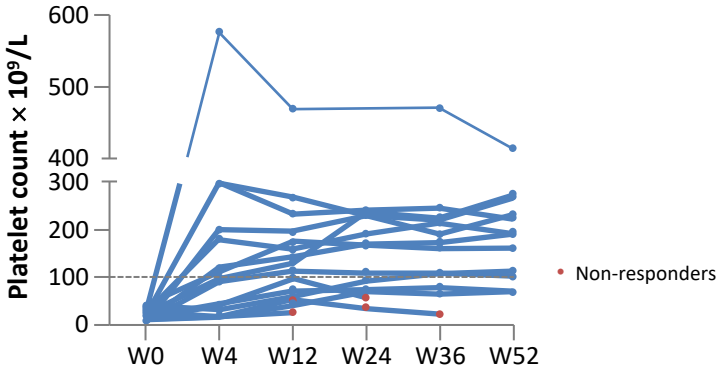
M, months; R, response.

Deshayes S, et al. Am J Hematol. 2019;94:1314-24.

Rituximab and ITP: rituximab + belimumab

- B cell activating factor is involved in the failure of rituximab in ITP
- Single-arm, prospective, phase 2b trial
- Rituximab at a fixed dose of 1 g 2 weeks apart combined with 5 infusions of belimumab at W0, W0 + 2 days, W4, W8, and W12
- 15 non-splenectomized adult ITP patients
- **At W52, 12 (80%) patients achieved an overall response**
- No severe AEs, infections, or severe hypogammaglobulinemia were observed

Efficacy of rituximab + belimumab in adults with persistent and chronic ITP



Outcome at W12	Outcome at W24	Outcome at W36	Outcome at W52
9 CR	9 CR	10 CR	10 CR
4 R	4 R	2 R	2 R
2 NR	2 NR	3 NR	3 NR

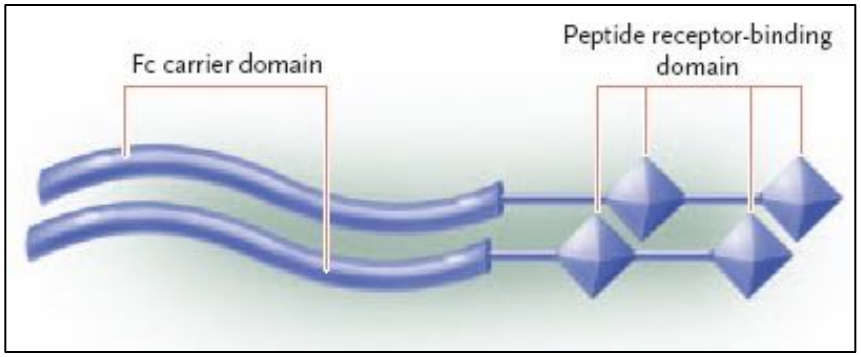
AE, adverse event; NR, no response.

Mahévas M, et al. Haematologica. 2020 Aug 6 [Epub ahead of print].

TPO-r mimetics

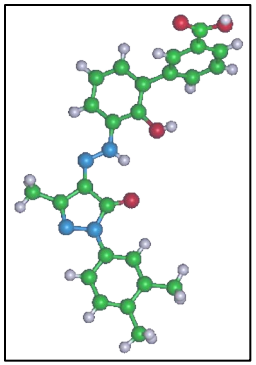
Romiplostim (Amgen)

AMG 531



Fc ↑ half-life
Subcutaneous injection once a week
Dosage 1 µg/kg to 10 µg/kg

Eltrombopag (Novartis)



Per os once a day
Dosage 50 to75 mg

TPO-mimetics and ITP

PROS

- **Evidence based medicine**
- Effective
- Effective in splenectomised patients
- Sustained response
- **Good short-term safety**
- Possible to switch
- **License**

CONS

- Continued use required?
- **Long-term safety?**
- Fluctuating effect
- **Cost**

UNMET NEEDS

- Mechanism of failure?
- Mechanism of fluctuating effect?
- Sustained response after withdrawal?

TPO mimetics: It is possible to switch

Khellaf *et al*, Haematologica 2013; 98: 881-7.
Gonzalez-Porras JR et al *et al*, Br J Haematol 2014
Kutter *el al*, Int J Hematol 2015

Platelet Disorders

ARTICLES

A retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia

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ABSTRACT

Romiplostim and eltrombopag, the first thrombopoietic receptor-agonists with demonstrated efficacy against immune thrombocytopenia in prospective controlled studies, were recently authorized in most countries for adults with chronic immune thrombocytopenia. So far, no data are available about the potential contribution of switching from romiplostim to eltrombopag or *vice versa* in terms of efficacy or tolerance. Efficacies and tolerance profiles were evaluated for 46 patients who sequentially received both drugs, switching from one to the other. The reasons for switching were: lack of efficacy for 23 patients, platelet-count fluctuations for 11, side effects for 4, and 8 patients' preferences. For 50-80% of the patients, switching from romiplostim to eltrombopag or eltrombopag to romiplostim effectively impacted the platelet count, with fluctuations disappearing in 54% and side effects resolved in 100%. In 80% of the patients, the 2 thrombopoietic receptor-agonists achieved similar response patterns. Our results confirmed that switching from one thrombopoietic receptor-agonist to the other could be beneficial in clinical practice for patients with severe chronic immune thrombopenia who failed to respond or experienced adverse events to the first. *(Clinical Trials.gov identifier: NCT01618734).*

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts responsible for various degrees of mucocutaneous bleeding.[1,2] ITP pathophysiology has long been considered to be only a matter of accelerated platelet destruction by platelet-bound antibodies but there is strong evidence to show that it is also associated with impaired platelet production.[3-11] Most therapies commonly used to treat ITP (e.g. corticosteroids, intravenous immunoglobulins (IVIg), immunosuppressants and splenectomy) are mainly active by reducing the destruction of antibody-coated platelets. In contrast, the novel thrombopoietic receptor-agonists (TPO-RAs) stimulate platelet production.

Two TPO-RAs are now available. Romiplostim is a peptide TPO-RA composed of an IgG Fc fragment to which four 14-amino–acid TPO peptides are attached; one of them activates the TPO-R by binding to the extracytoplasmic domain, just like endogenous TPO.[12] Romiplostim is administered as a weekly subcutaneous injection.[13] Eltrombopag is a non-peptide TPO-RA that is a 442-Da drug that binds to a transmembrane site on the TPO-R, thereby activating it. It is administered daily as an oral tablet.[14] In randomized-controlled trials, the reported response rates to romiplostim and eltrombopag were 59-88% and this high efficacy was achieved in splenectomized and non-splenectomized ITP patients.[15-19] In view of these robust data, both drugs have been approved for adult chronic ITP in more than 80 countries and some groups consider them second-line treatment for chronic ITP.[20,21] However, in Europe, they are only authorized for use after splenectomy failure or when splenectomy is contraindicated.

In contrast to these very good results, in an observational study on romiplostim we showed that inefficacy or side effects led approximately one-third of the patients to discontinue treatment.[22] Because romiplostim and eltrombopag bind to different sites on the TPO-R and the 2 molecules have not yet been directly compared, the relevance of switching from one TPO-RA to the other in clinical practice has not been

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bjh research paper

Use of eltrombopag after romiplostim in primary immune thrombocytopenia

José Ramón González-Porras,[1] María Eva Mingot-Castellano,[1] Marcio M. Andrade,[1] Rafael Alonso,[1] Isabel Caparrós,[2] María Carmen Arratibel,[3] Fernando Fernández-Fuertes,[4] María José Curtti,[4] Cristina Pascual,[5] Blanca Sánchez-González,[6] Silvia Bernat,[11] Miguel Angel Fuertes-Palacio,[12] Juan Andrés Vázquez-Paganini,[13] Pavel E. Olivera,[14] María Teresa Alvarez-Román,[15] Isidro Jarque,[16] Montserrat Cortés,[17] Violeta Martínez-Robles,[18] Francisco Javier Díaz-Gálvez,[19] María Calbacho,[20] Carmen Fernández-Miñano,[21] Javier García-Frade[22] and Tomás José González-López[23]

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Summary

The thrombopoietin receptor agonists (THPO-RAs), romiplostim and eltrombopag, are effective and safe in immune thrombocytopenia (ITP). However, the value of their sequential use when no response is achieved or when adverse events occur with one THPO-RA has not been clearly established. Here we retrospectively evaluated 51 primary ITP adult patients treated with romiplostim followed by eltrombopag. The median age of our cohort was 49 (range, 18–83) years. There were 32 women and 19 men. The median duration of romiplostim use before switching to eltrombopag was 12 (interquartile range 5–21) months. The reasons for switching were: lack of efficacy ($n = 25$), patient preference ($n = 16$), platelet-count fluctuation ($n = 6$) and side-effects ($n = 4$). The response rate to eltrombopag was 80% (41/51), including 67% ($n = 35$) complete responses. After a median follow-up of 14 months, 31 patients maintained their response. Efficacy was maintained after switching in all patients in the patient preference, platelet-count fluctuation and side-effect groups. 33% of patients experienced one or more adverse events during treatment with eltrombopag. We consider the use of eltrombopag after romiplostim for treating ITP to be effective and safe. Response to eltrombopag was related to the cause of romiplostim discontinuation.

Keywords: immune thrombocytopenia, eltrombopag, romiplostim, efficacy, switching.

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Int J Hematol (2015) 101:255–263
DOI 10.1007/s12185-014-1731-7

ORIGINAL ARTICLE

Treatment patterns and clinical outcomes in patients with chronic immune thrombocytopenia (ITP) switched to eltrombopag or romiplostim

David J. Kuter · Cynthia Macahilig · Kelly M. Grotzinger · Sara A. Poston · Peter Feng Wang · Katie L. Dawson · Melea Ward

Received: 3 November 2014 / Revised: 16 December 2014 / Accepted: 19 December 2014 / Published online: 14 January 2015

Abstract This observational study aimed to assess real-world treatment patterns and clinical outcomes for patients with chronic immune thrombocytopenia (ITP) currently being treated with eltrombopag or romiplostim after switching from corticosteroids, rituximab, or the alternate thrombopoietin receptor agonist (TPO-RA). The study examined the rationale for switching to TPO-RA therapy using aided responses. Dosing patterns were also analyzed before and after switching. Treatment outcomes were assessed through platelet counts at multiple time points including treatment initiation and after switching at the last office visit. A total of 280 patients were enrolled whose active therapy for ITP was replaced with either eltrombopag ($n = 130$) or romiplostim ($n = 150$). Efficacy-related issues (desired platelet count not achieved and/or lack of response to prior therapy) were the main drivers for therapy switching among all patients (54 % for eltrombopag vs. 57 % for romiplostim). Platelet counts at the last office visit showed improvement compared with counts at the initiation of either eltrombopag or romiplostim treatment. No significant differences were noted when comparing clinical outcomes between the eltrombopag and romiplostim treatment cohorts. Our results suggest that switching to the other TPO-RA may be beneficial if there is inadequate response to treatment with the initial TPO-RA.

Keywords Clinical outcomes · Eltrombopag · Immune thrombocytopenia · Romiplostim · Treatment switching

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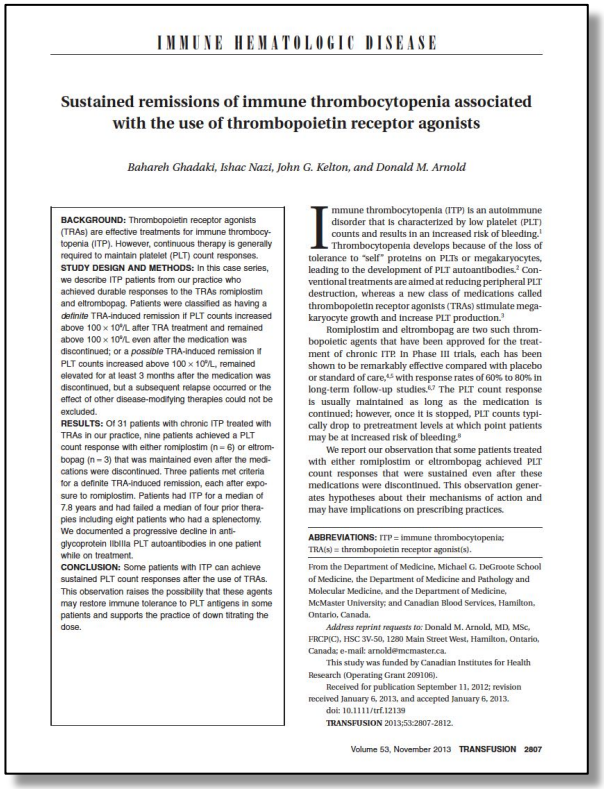
Introduction

Immune thrombocytopenia (ITP) is estimated to affect 60,000 adult patients in the United States [1]. It is characterized by low platelet counts and the attendant risk of bleeding. For patients with chronic ITP, the persistently low platelet counts present real and perceived risks for serious and even fatal bleeding events [2], and may therefore require emergency department visits and hospitalization [3]. Decreased platelet counts, disease symptoms, and treatment side effects have a notable impact on the overall quality of life for patients with ITP [2, 4–7].

Standard first-line therapy for the treatment of ITP includes corticosteroids, anti-D/anti-RhD immunoglobulin, or intravenous immunoglobulins (IVIg) [8, 9]. Corticosteroids are usually only given for a few months

Sustained response after stopping TPO-RAs is possible



IMMUNE HEMATOLOGIC DISEASE

Sustained remissions of immune thrombocytopenia associated with the use of thrombopoietin receptor agonists

Bahareh Ghadaki, Ishac Nazi, John G. Kelton, and Donald M. Arnold

BACKGROUND: Thrombopoietin receptor agonists (TRAs) are effective treatments for immune thrombocytopenia (ITP). However, continuous therapy is generally required to maintain platelet (PLT) count responses.
STUDY DESIGN AND METHODS: In this case series, we describe ITP patients from our practice who achieved durable responses to the TRAs romiplostim and eltrombopag. Patients were classified as having a *definite* TRA-induced remission if PLT counts increased above 100×10^9/L after TRA treatment and remained above 100×10^9/L even after the medication was discontinued; or a *possible* TRA-induced remission if PLT counts increased above 100×10^9/L, remained elevated for at least 3 months after the medication was discontinued, but a subsequent relapse occurred or the effect of other disease-modifying therapies could not be excluded.
RESULTS: Of 31 patients with chronic ITP treated with TRAs in our practice, nine patients achieved a PLT count response with either romiplostim (n = 6) or eltrombopag (n = 3) that was maintained even after the medications were discontinued. Three patients met criteria for a definite TRA-induced remission, each after exposure to romiplostim. Patients had ITP for a median of 7.8 years and had failed a median of four prior therapies including eight patients who had a splenectomy. We documented a progressive decline in anti-glycoprotein IIb/IIIa PLT autoantibodies in one patient while on treatment.
CONCLUSION: Some patients with ITP can achieve sustained PLT count responses after the use of TRAs. This observation raises the possibility that these agents may restore immune tolerance to PLT antigens in some patients and supports the practice of down titrating the dose.

Immune thrombocytopenia (ITP) is an autoimmune disorder that is characterized by low platelet (PLT) counts and results in an increased risk of bleeding.[1] Thrombocytopenia develops because of the loss of tolerance to "self" proteins on PLTs or megakaryocytes, leading to the development of PLT autoantibodies.[2] Conventional treatments are aimed at reducing peripheral PLT destruction, whereas a new class of medications called thrombopoietin receptor agonists (TRAs) stimulate megakaryocyte growth and increase PLT production.[3]

Romiplostim and eltrombopag are two such thrombopoietic agents that have been approved for the treatment of chronic ITP. In Phase III trials, each has been shown to be remarkably effective compared with placebo or standard of care,[4,5] with response rates of 60% to 80% in long-term follow-up studies.[6,7] The PLT count response is usually maintained as long as the medication is continued; however, once it is stopped, PLT counts typically drop to pretreatment levels at which point patients may be at increased risk of bleeding.[8]

We report our observation that some patients treated with either romiplostim or eltrombopag achieved PLT count responses that were sustained even after these medications were discontinued. This observation generates hypotheses about their mechanisms of action and may have implications on prescribing practices.

ABBREVIATIONS: ITP = immune thrombocytopenia; TRA(s) = thrombopoietin receptor agonist(s).

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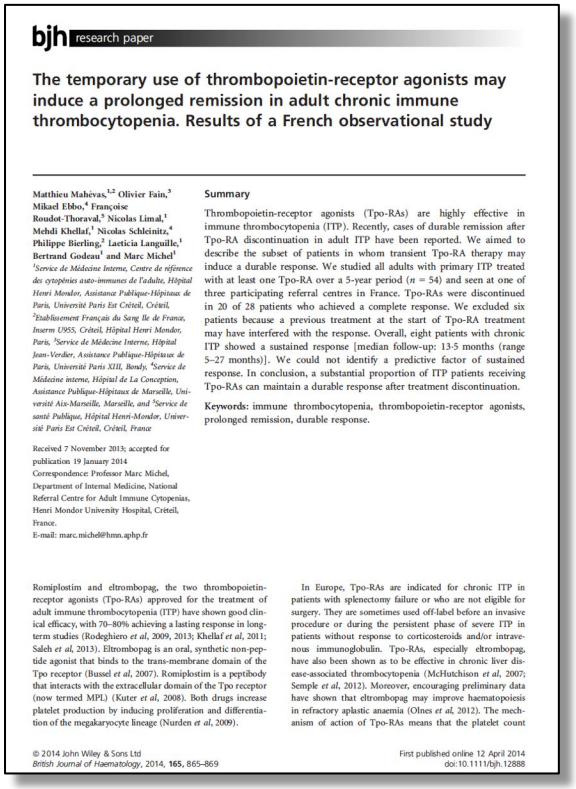

bjh research paper

The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study

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Summary

Thrombopoietin-receptor agonists (Tpo-RAs) are highly effective in immune thrombocytopenia (ITP). Recently, cases of durable remission after Tpo-RA discontinuation in adult ITP have been reported. We aimed to describe the subset of patients in whom transient Tpo-RA therapy may induce a durable response. We studied all adults with primary ITP treated with at least one Tpo-RA over a 5-year period (n = 54) and seen at one of three participating referral centres in France. Tpo-RAs were discontinued in 20 of 28 patients who achieved a complete response. We excluded six patients because a previous treatment at the start of Tpo-RA treatment may have interfered with the response. Overall, eight patients with chronic ITP showed a sustained response [median follow-up: 13·5 months (range 5–27 months)]. We could not identify a predictive factor of sustained response. In conclusion, a substantial proportion of ITP patients receiving Tpo-RAs can maintain a durable response after treatment discontinuation.

Keywords: immune thrombocytopenia, thrombopoietin-receptor agonists, prolonged remission, durable response.

Romiplostim and eltrombopag, the two thrombopoietin-receptor agonists (Tpo-RAs) approved for the treatment of adult immune thrombocytopenia (ITP) have shown good clinical efficacy, with 70–80% achieving a lasting response in long-term studies (Rodeghiero *et al*, 2009, 2013; Khellaf *et al*, 2011; Saleh *et al*, 2013). Eltrombopag is an oral, synthetic non-peptide agonist that binds to the trans-membrane domain of the Tpo receptor (Bussel *et al*, 2007). Romiplostim is a peptibody that interacts with the extracellular domain of the Tpo receptor (now termed MPL) (Kuter *et al*, 2008). Both drugs increase platelet production by inducing proliferation and differentiation of the megakaryocyte lineage (Nurden *et al*, 2009).

In Europe, Tpo-RAs are indicated for chronic ITP in patients with splenectomy failure or who are not eligible for surgery. They are sometimes used off-label before an invasive procedure or during the persistent phase of severe ITP in patients without response to corticosteroids and/or intravenous immunoglobulin. Tpo-RAs, especially eltrombopag, have also been shown as to be effective in chronic liver disease-associated thrombocytopenia (McHutchison *et al*, 2007; Semple *et al*, 2012). Moreover, encouraging preliminary data have shown that eltrombopag may improve haematopoiesis in refractory aplastic anaemia (Olnes *et al*, 2012). The mechanism of action of Tpo-RAs means that the platelet count

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RESEARCH ARTICLE

AJH

Successful discontinuation of eltrombopag after complete remission in patients with primary immune thrombocytopenia

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Eltrombopag is effective and safe in immune thrombocytopenia (ITP). Some patients may sustain their platelet response when treatment is withdrawn but the frequency of this phenomenon is unknown. We retrospectively evaluated 260 adult primary ITP patients (165 women and 95 men; median age, 62 years) treated with eltrombopag after a median time from diagnosis of 24 months. Among the 201 patients who achieved a complete remission (platelet count >100 × 10^9/l), eltrombopag was discontinued in 80 patients. Reasons for eltrombopag discontinuation were: persistent response despite a reduction in dose over time (n = 33), platelet count >400 × 10^9/l (n = 29), patient's request (n = 5), elevated aspartate aminotransferase (n = 3), diarrhea (n = 3), thrombosis (n = 3), and other reasons (n = 4). Of the 49 evaluable patients, 26 patients showed sustained response after discontinuing eltrombopag without additional ITP therapy, with a median follow-up of 9 (range, 6–25) months. These patients were characterized by a median time since ITP diagnosis of 46.5 months, with 4/26 having ITP<1 year. Eleven patients were male and their median age was 59 years. They received a median of 4 previous treatment lines and 42% were splenectomized. No predictive factors of sustained response after eltrombopag withdrawal were identified. Platelet response following eltrombopag cessation may be sustained in an important percentage of adult primary ITP patients who achieved CR with eltrombopag. However, reliable markers for predicting which patients will have this response are needed.

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Conflict of interest: Nothing to report
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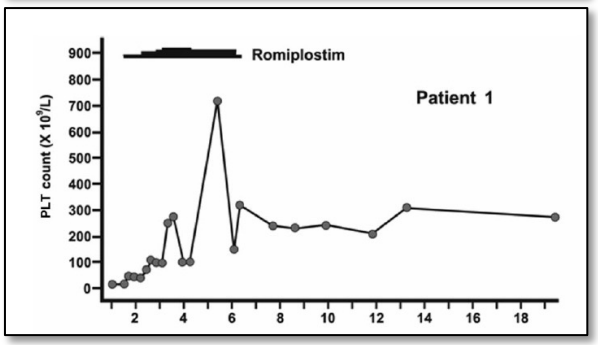


Patient 1: 59-year-old female. Romiplostim at a starting dose of 1.0 mg/kg. ITP for 7.8 years and she received 5 prior ITP treatments, including splenectomy 5 years earlier. Before starting romiplostim, the PLT count was 20 G/L.

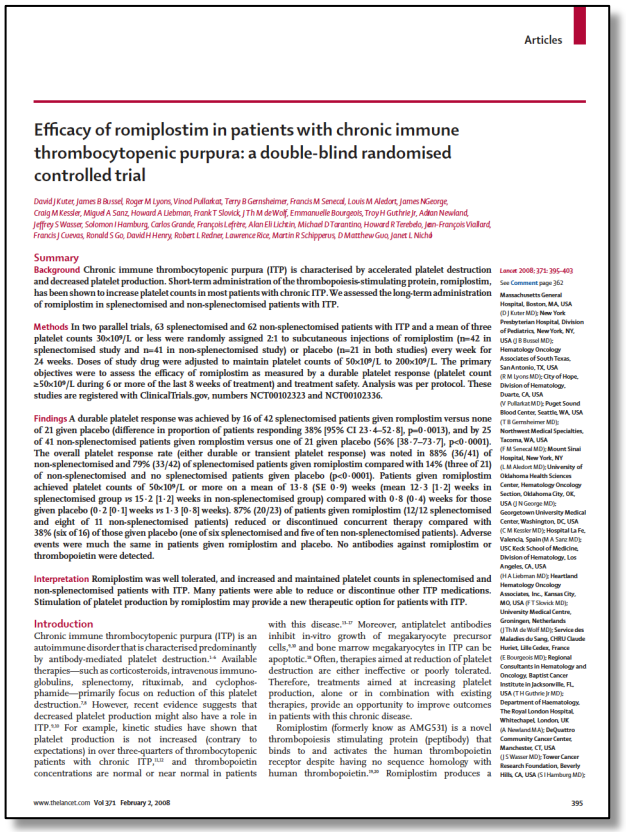
Ghadaki *et al*, ***Transfusion*** 2013; 53: 2807-2812

Mahévas *et al*, **Br J Haematol** 2014; 165: 865-9

Gonzales-Lopez *et al*, **Am J Hematol** 2015; 90: E40-E43.

TPO-r+, can we increase the dose ?

Kutter *et al*, **Lancet** 2008; 371:395-403



Articles

Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial

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Summary

Background Chronic immune thrombocytopenic purpura (ITP) is characterised by accelerated platelet destruction and decreased platelet production. Short-term administration of the thrombopoiesis-stimulating protein, romiplostim, has been shown to increase platelet counts in most patients with chronic ITP. We assessed the long-term administration of romiplostim in splenectomised and non-splenectomised patients with ITP.

Methods In two parallel trials, 63 splenectomised and 62 non-splenectomised patients with ITP and a mean of three platelet counts 30×10^9/L or less were randomly assigned 2:1 to subcutaneous injections of romiplostim (n=42 in splenectomised study and n=41 in non-splenectomised study) or placebo (n=21 in both studies) every week for 24 weeks. Doses of study drug were adjusted to maintain platelet counts of 50×10^9/L to 200×10^9/L. The primary objectives were to assess the efficacy of romiplostim as measured by a durable platelet response (platelet count $\geq50\times10^9$/L during 6 or more of the last 8 weeks of treatment) and treatment safety. Analysis was per protocol. These studies are registered with ClinicalTrials.gov, numbers NCT00102323 and NCT00102336.

Findings A durable platelet response was achieved by 16 of 42 splenectomised patients given romiplostim versus none of 21 given placebo (difference in proportion of patients responding 38% [95% CI 23·4–52·8], p=0·0013), and by 25 of 41 non-splenectomised patients given romiplostim versus one of 21 given placebo (56% [38·7–73·7], p<0·0001). The overall platelet response rate (either durable or transient platelet response) was noted in 88% (36/41) of non-splenectomised and 79% (33/42) of splenectomised patients given romiplostim compared with 14% (three of 21) of non-splenectomised and no splenectomised patients given placebo (p<0·0001). Patients given romiplostim achieved platelet counts of 50×10^9/L or more on a mean of 13·8 (SE 0·9) weeks (mean 12·3 [1·2] weeks in splenectomised group *vs* 15·2 [1·2] weeks in non-splenectomised group) compared with 0·8 (0·4) weeks for those given placebo (0·2 [0·1] weeks *vs* 1·3 [0·8] weeks). 87% (20/23) of patients given romiplostim (12/12 splenectomised and eight of 11 non-splenectomised patients) reduced or discontinued concurrent therapy compared with 38% (six of 16) of those given placebo (one of six splenectomised and five of ten non-splenectomised patients). Adverse events were much the same in patients given romiplostim and placebo. No antibodies against romiplostim or thrombopoietin were detected.

Interpretation Romiplostim was well tolerated, and increased and maintained platelet counts in splenectomised and non-splenectomised patients with ITP. Many patients were able to reduce or discontinue other ITP medications. Stimulation of platelet production by romiplostim may provide a new therapeutic option for patients with ITP.

Lancet 2008; 371: 395–403

See Comment page 362

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Romiplostim 15µg/kg.bw

Olmes *et al*, **NEJM** 2012; 367:11-19

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Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

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ABSTRACT

BACKGROUND

Severe aplastic anemia, which is characterized by immune-mediated bone marrow hypoplasia and pancytopenia, can be treated effectively with immunosuppressive therapy or allogeneic transplantation. One third of patients have disease that is refractory to immunosuppression, with persistent, severe cytopenia and a profound deficit in hematopoietic stem cells and progenitor cells. Thrombopoietin may increase the number of hematopoietic stem cells and progenitor cells.

METHODS

We conducted a phase 2 study involving patients with aplastic anemia that was refractory to immunosuppression to determine whether the oral thrombopoietin mimetic eltrombopag (Promacta) can improve blood counts. Twenty-five patients received eltrombopag at a dose of 50 mg, which could be increased, as needed, to a maximum dose of 150 mg daily, for a total of 12 weeks. Primary end points were clinically significant changes in blood counts or transfusion independence. Patients with a response continued to receive eltrombopag.

RESULTS

Eleven of 25 patients (44%) had a hematologic response in at least one lineage at 12 weeks, with minimal toxic effects. Nine patients no longer needed platelet transfusions (median increase in platelet count, 44,000 per cubic millimeter). Six patients had improved hemoglobin levels (median increase, 4.4 g per deciliter); 3 of them were previously dependent on red-cell transfusions and no longer needed transfusions. Nine patients had increased neutrophil counts (median increase, 1350 per cubic millimeter). Serial bone marrow biopsies showed normalization of trilineage hematopoiesis in patients who had a response, without increased fibrosis. Monitoring of immune function revealed no consistent changes.

CONCLUSIONS

Treatment with eltrombopag was associated with multilineage clinical responses in some patients with refractory severe aplastic anemia. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00922883.)

From the Hematology Branch (M.J.O., P.S., R.D., Y.T., B.D., A.R.P., S.S., X.F., N.S.Y., C.E.D.) and the Office of Biostatistics Research (C.O.W.), National Heart, Lung, and Blood Institute; the Hematology Section, Department of Laboratory Medicine, Mark O. Hatfield Clinical Research Center (K.R.C., J.L.); and the Trans-NIH Center for Human Immunology, Autoimmunity, and Inflammation (A.B.); National Institutes of Health, Bethesda, MD. Address reprint requests to Dr. Dunbar at the Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bldg. 10 CRC 4E-5132, Bethesda, MD 20892, or at dunbarc@nhlbi.nih.gov.

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Eltrombopag 300mg/d

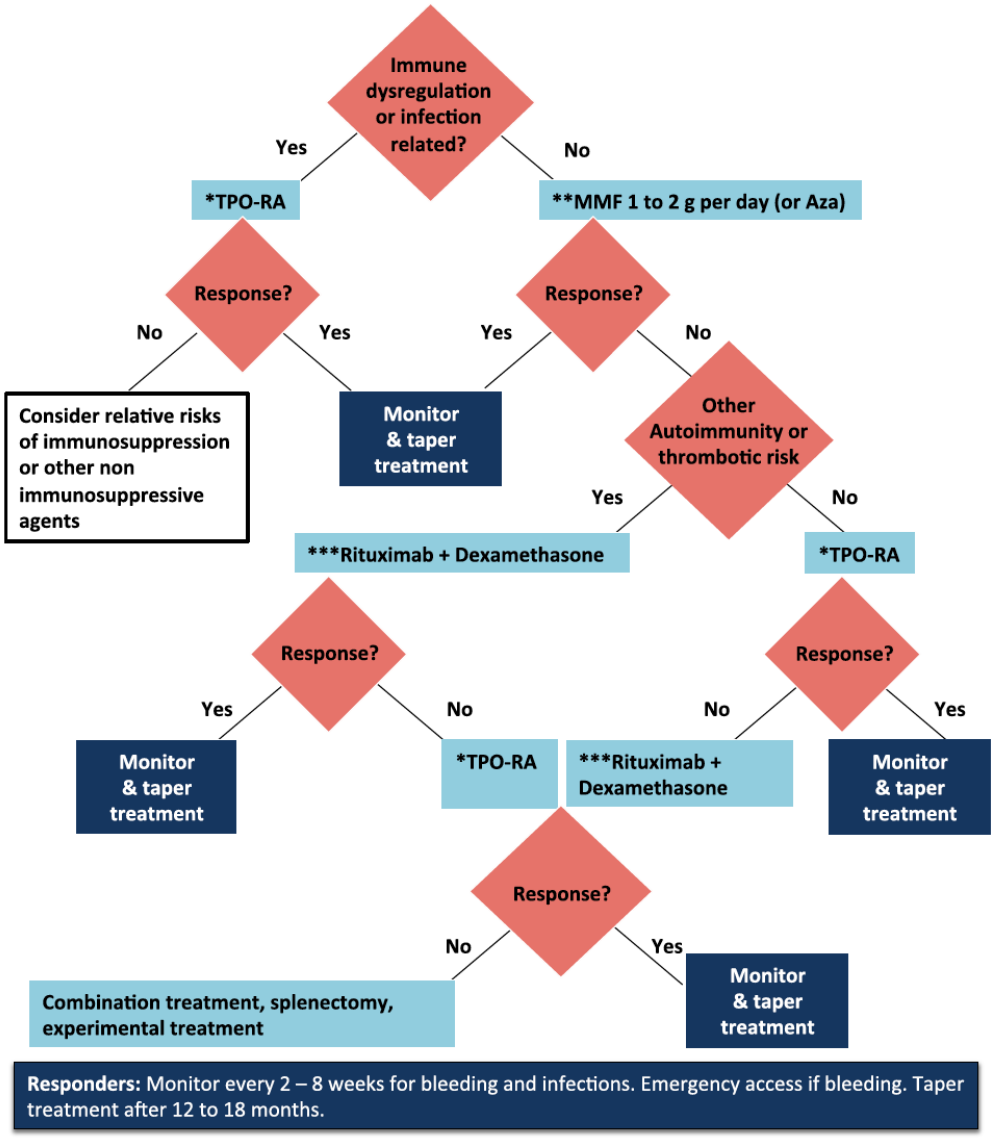
TPO mimetics in the real life….

- Can we use it during pregnancy? **NO**
- Can we use it if renal failure? **YES**
- Can we use it if liver disease? **BE CAREFUL**
- I want to stop it: **NOT ABRUPTLY**
- What can we do if thrombosis: **????**
- Is a good option for SLE and/or APS: **NO (+/-)**
- Is a good option for emergency: **YES and NO**
- Is a good option for elderly: **WHY NOT**

State of the art – how I manage immune thrombocytopenia

Nichola Cooper

British Journal of Haematology, 2017, **177,** 39–54



Mycophenolate Mofetil for First-Line Treatment of Immune Thrombocytopenia

- Multicenter open-label, randomized, controlled trial
- **Glucocorticoid alone vs MMF combined with glucocorticoid** 25–75 mg for 12 weeks plus pulsed **dexamethasone**, 40 mg daily for four consecutive days every four weeks for 1–3 courses
- Primary endpoint: Treatment failure after 2 years of FU
- 120 patients included, **13 (22%) exhibited failure in MMF group vs 27 (44%) in the GC group (P=0.008)**
- Worse HQL in MMF group

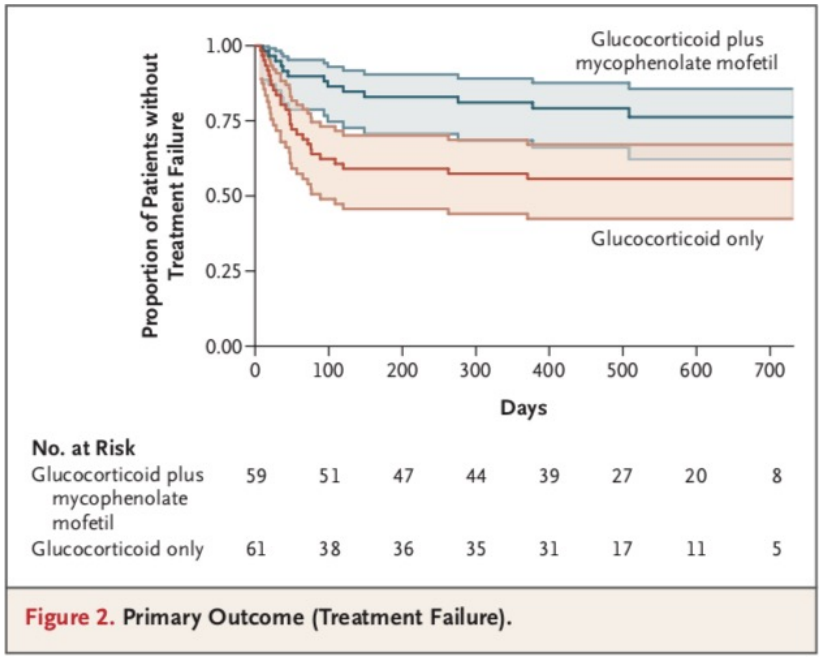


Figure 2. Primary Outcome (Treatment Failure).

Bradbury et al, NEJM 2021

Splenectomy is still indicated for ITP!

PROS

- Experience!!!
- Effective!!!
- Safe, and possible to prevent complications
- Low cost
- Respect of ASH guidelines and « *licence* »

BUT UNMET NEEDS…

- Long-term response???
- Long-term safety???
- Value of isotopic study to predict sustained response?

Complications of splenectomy

- **Infection**
- Malignancy?
- **Vascular complications**
  - Arterio**thrombosis**
  - Venous **thrombosis**
  - Cardiovascular events
  - Pulmonary hypertension

Review article

Vascular complications after splenectomy for hematologic disorders

Shelley E. Crary[1] and George R. Buchanan[1]

[1]Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas

The most widely recognized long-term risk of splenectomy is overwhelming bacterial infection. More recently, thrombosis has become appreciated as another potential complication of the procedure. Because of these long-term risks, the indications for and timing of splenectomy are debated in the medical community. Accordingly, the adverse effects and benefits of splenectomy for hematologic disorders and other conditions demand further study. This comprehensive review summarizes the existing literature pertaining to vascular complications after splenectomy for hematologic conditions and attempts to define the potential pathophysiologic mechanisms involved. This complex topic encompasses diverse underlying conditions for which splenectomy is performed, diverse thrombotic complications, and multiple pathophysiologic mechanisms. (Blood. 2009;114: 2861-2868)

Introduction

The spleen was once considered unnecessary for life; however, it clearly serves extremely important hematologic and immunologic functions. The spleen is separated into 2 major functional compartments: the white pulp and the red pulp. The white pulp contains a large mass of lymphoid tissue and serves a vital role in the recognition of antigens and production of antibodies. The red pulp of the spleen consists of a tight meshwork of sinusoids, the cords of Billroth, which primarily serve hematologic functions, especially filtration of the blood. The milieu of the red pulp is relatively acidic and hypoglycemic. Aged or damaged red cells not able to tolerate this harsh environment are ultimately removed by splenic macrophages. Antibody-coated cells and bacteria are also recognized and ingested by these phagocytic cells lining the sinusoids. Therefore, persons without a functioning spleen have a severe impairment in their ability to clear encapsulated organisms from the bloodstream. Particulate matter is also removed from red cells as they pass through the splenic sinusoids, and "polished" or "conditioned" red cells, free of surface imperfections, are returned to the bloodstream. The red pulp also acts as a reservoir for approximately one-third of the total platelet mass and a smaller proportion of granulocytes.

Asplenia and hyposplenia

Congenital asplenia can occur in isolation or may be associated with certain forms of congenital heart defects or heterotaxy syndromes.[1] Children with sickle cell disease have acquired hyposplenism that begins at several months of age and progresses to splenic infarction. Young patients with sickle cell disease may also develop recurrent and even life-threatening splenic sequestration requiring surgical splenectomy. Moreover, many immunologic and rheumatic disorders are associated with impairment of the spleen's phagocytic and immunologic functions. Transient functional hyposplenism may also occur during therapy with corticosteroids and after pharmaceutical reticuloendothelial blockade with intravenous IgG or anti-D immunoglobulin.

Surgical splenectomy

According to the National Hospital Discharge Survey, approximately 22 000 total splenectomies were performed for all causes in the United States during 2005.[2] In most institutions, trauma and incidental splenectomy are the primary indications,[3] although splenectomy for trauma is becoming less common than in years past, resulting from more conservative nonoperative management of splenic injury.[4] The most frequent medical indication for splenectomy is a hematologic disorder (Table 1). Splenectomy is performed in patients having hemolytic anemia (eg, hereditary spherocytosis [HS] and autoimmune hemolytic anemia) because the intrinsically abnormal or antibody-coated red blood cells are prematurely destroyed by splenic macrophages. Because splenectomy can ameliorate the underlying anemia, it is often considered the treatment of choice for such conditions. Sickle cell disease may be complicated by splenic sequestration requiring surgical splenectomy, and patients with β-thalassemia may undergo splenectomy to relieve splenomegaly resulting in increased destruction of red blood cells. Splenectomy is also performed in patients with immune thrombocytopenic purpura (ITP), especially when chronic or severe.

Septic risk of asplenia and hyposplenism

For decades, it has been known that in persons with asplenia the major long-term complication is overwhelming bacterial sepsis.[5,6] These infections occur in persons after surgical splenectomy as well as in conditions predisposing to hyposplenism or asplenia. This complication is less frequent than in years past as a result of pneumococcal vaccination, prophylactic penicillin, and prompt administration of parenteral antibiotics when fever occurs.

Submitted April 2, 2009; accepted July 13, 2009. Prepublished online as *Blood* First Edition paper, July 27, 2009; DOI 10.1182/blood-2009-04-210112.

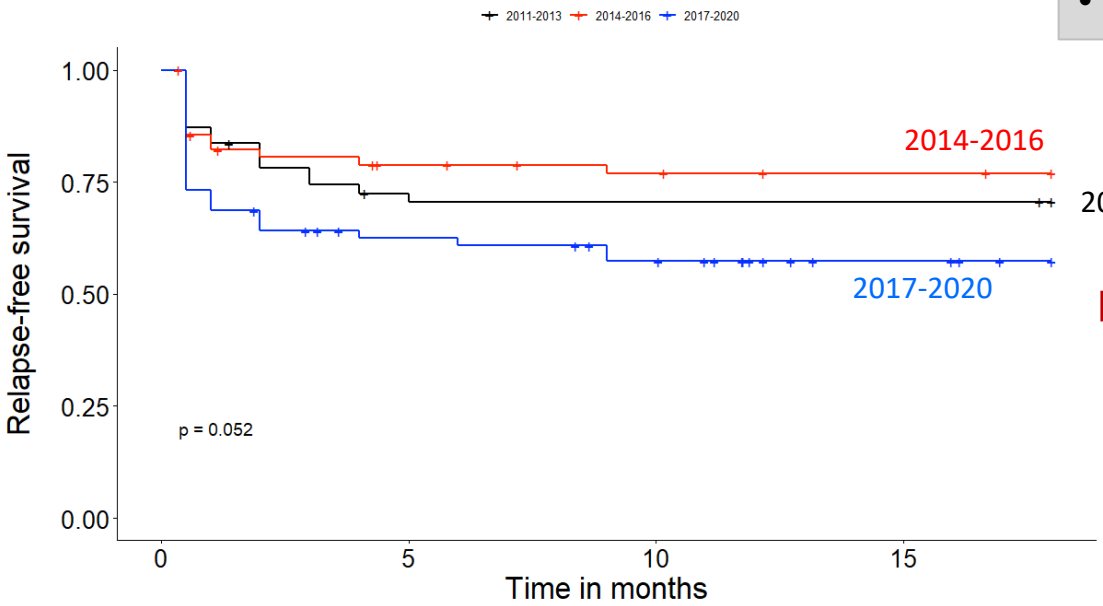
Crary S and Buchanan G. *Blood* 2009;114:2861–8; Vianelli N, *et al*. *Haematologica* 2012;98:875–80; Kristinsson S, *et al*. *Haematologica* 2014;99:392–8; Ruggeri M, *et al. J Thromb Haemost* 2014;12:1266–73.

Results

- **Initial response**: 144/185 (77.8%)
- **Relapse:** 23/144 (12.4%)
- **Sustained response:** 121 (65.4%)

Percentage of response to splenectomy according to pattern of response of previous treatments

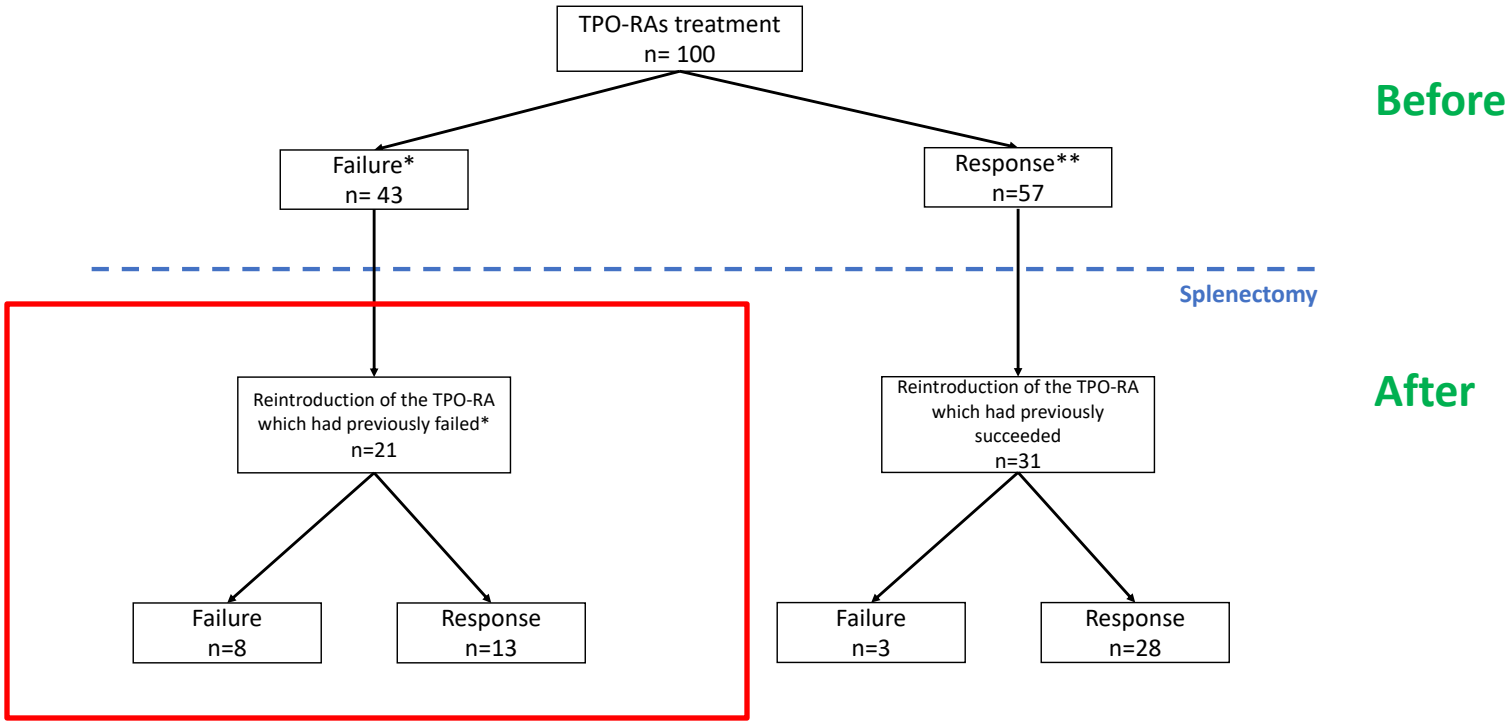
- If TPO-RA failure: 50%
- If TPO-RA + Rituximab failure: 46%
- If > 6 drugs before splenectomy: 46%



Trend to worse response during the last period

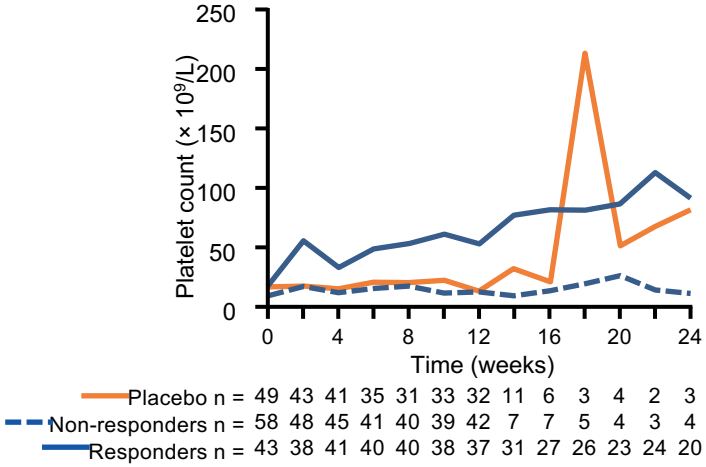
Results

Pattern of response to TPO-RAs before and after splenectomy

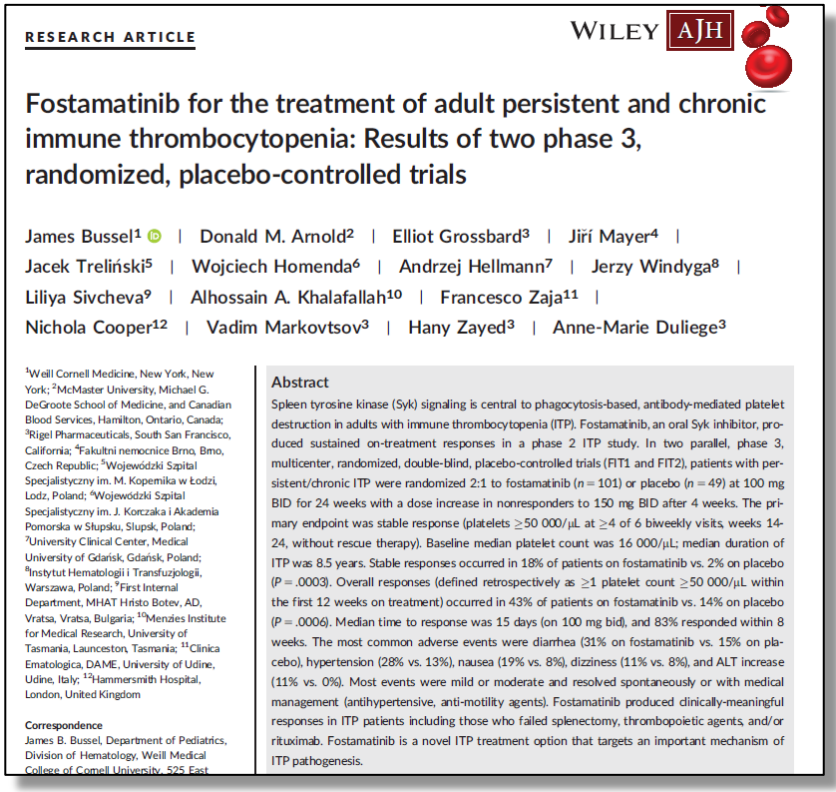


Fostamatinib for treatment of adult persistent and chronic ITP: results of two Phase 3, randomised, placebo-controlled trials

Patients with chronic ITP (duration >5 years) and **refractory to several therapeutic options** (spl 35%, RTX 32%, IS 44%)



	Placebo	Fostamatinib
Stable response	2%	18%
Overall response	14%	43%



RESEARCH ARTICLE

WILEY AJH

Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials

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Abstract

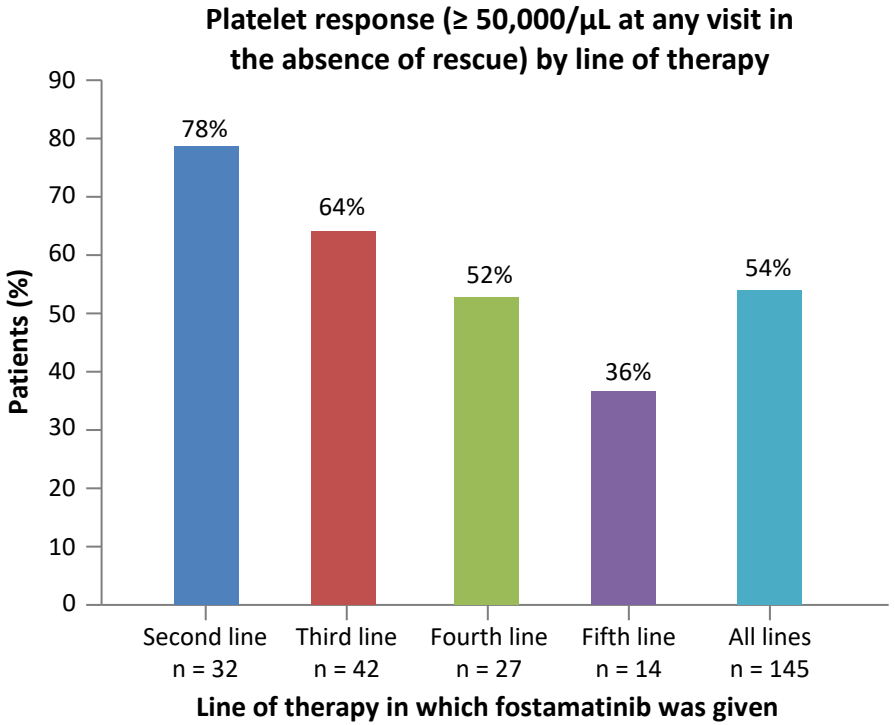
Spleen tyrosine kinase (Syk) signaling is central to phagocytosis-based, antibody-mediated platelet destruction in adults with immune thrombocytopenia (ITP). Fostamatinib, an oral Syk inhibitor, produced sustained on-treatment responses in a phase 2 ITP study. In two parallel, phase 3, multicenter, randomized, double-blind, placebo-controlled trials (FIT1 and FIT2), patients with persistent/chronic ITP were randomized 2:1 to fostamatinib ($n = 101$) or placebo ($n = 49$) at 100 mg BID for 24 weeks with a dose increase in nonresponders to 150 mg BID after 4 weeks. The primary endpoint was stable response (platelets ≥50 000/μL at ≥4 of 6 biweekly visits, weeks 14-24, without rescue therapy). Baseline median platelet count was 16 000/μL; median duration of ITP was 8.5 years. Stable responses occurred in 18% of patients on fostamatinib vs. 2% on placebo ($P = .0003$). Overall responses (defined retrospectively as ≥1 platelet count ≥50 000/μL within the first 12 weeks on treatment) occurred in 43% of patients on fostamatinib vs. 14% on placebo ($P = .0006$). Median time to response was 15 days (on 100 mg bid), and 83% responded within 8 weeks. The most common adverse events were diarrhea (31% on fostamatinib vs. 15% on placebo), hypertension (28% vs. 13%), nausea (19% vs. 8%), dizziness (11% vs. 8%), and ALT increase (11% vs. 0%). Most events were mild or moderate and resolved spontaneously or with medical management (antihypertensive, anti-motility agents). Fostamatinib produced clinically-meaningful responses in ITP patients including those who failed splenectomy, thrombopoietic agents, and/or rituximab. Fostamatinib is a novel ITP treatment option that targets an important mechanism of ITP pathogenesis.

Bussel J, et al. Am J Hematol 2018;93:921–30.

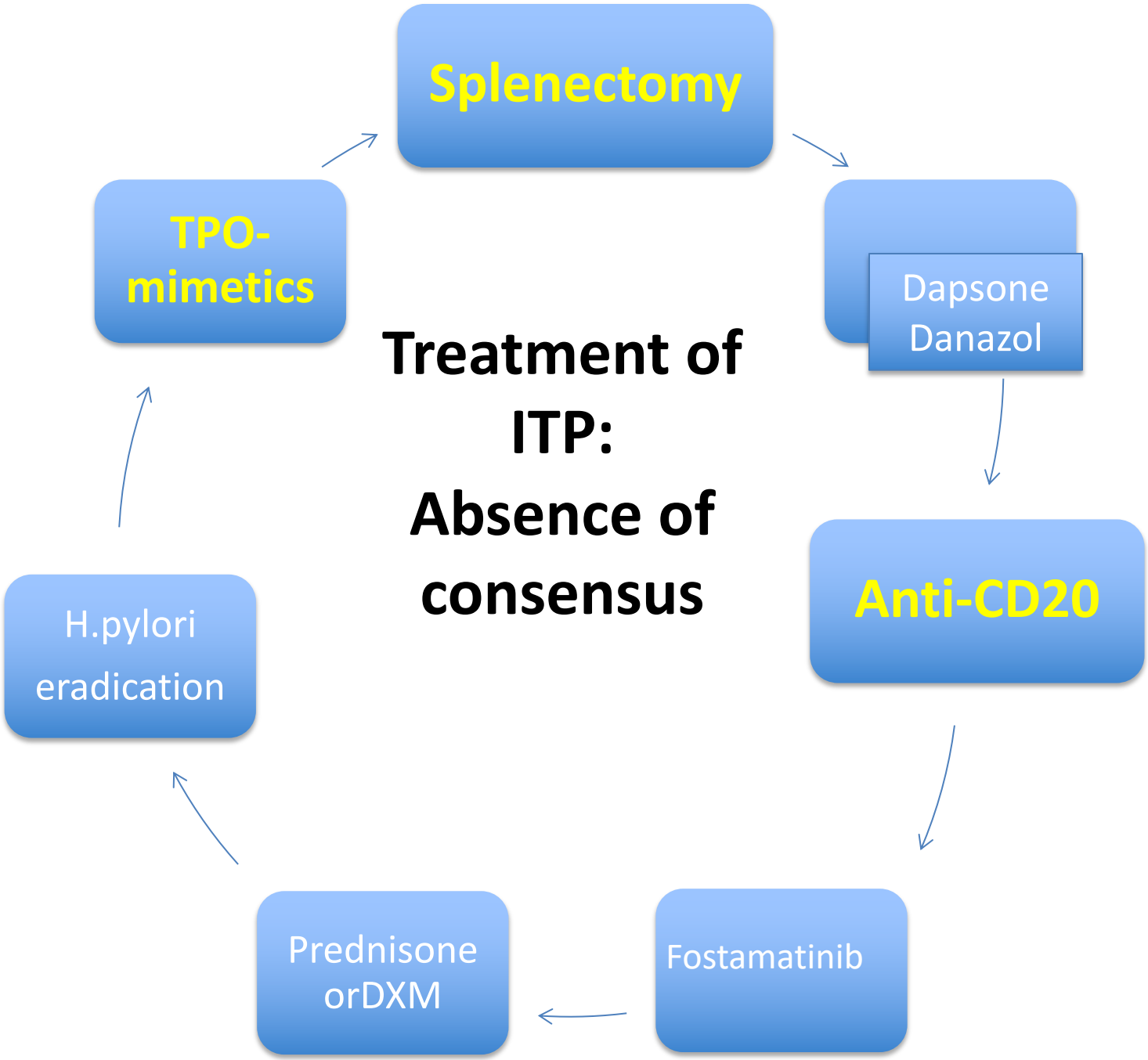
IS, immunosuppressant.

Fostamatinib and ITP: post-hoc analysis of the phase 3 clinical study data

- Evaluated the response in ITP patients for whom fostamatinib was second-line therapy as well as third-, fourth-, or fifth-line therapy
- **Platelet response rate was 78%** in second-line therapy patients and decreased with each successive line of therapy
- **The most common AEs** in the 32 second-line therapy patients vs the total population were **hypertension** (31% vs 22%), **diarrhea** (25% vs 36%), and **upper respiratory tract infection** (16% vs 12%)



Cooper N, et al. Br J Haematol, 2020, 190, 933–938


Splenectomy
Dapsone
Danazol
Anti-CD20
Fostamatinib
Prednisone
orDXM
H.pylori
eradication
TPO-
mimetics
Treatment of
ITP:
Absence of
consensus

Factors that may influence the choice of treatment

- Patient and physician's preferences
- Co-morbidities, age
- Cost
- Restrictions imposed by health funding authorities or insurance

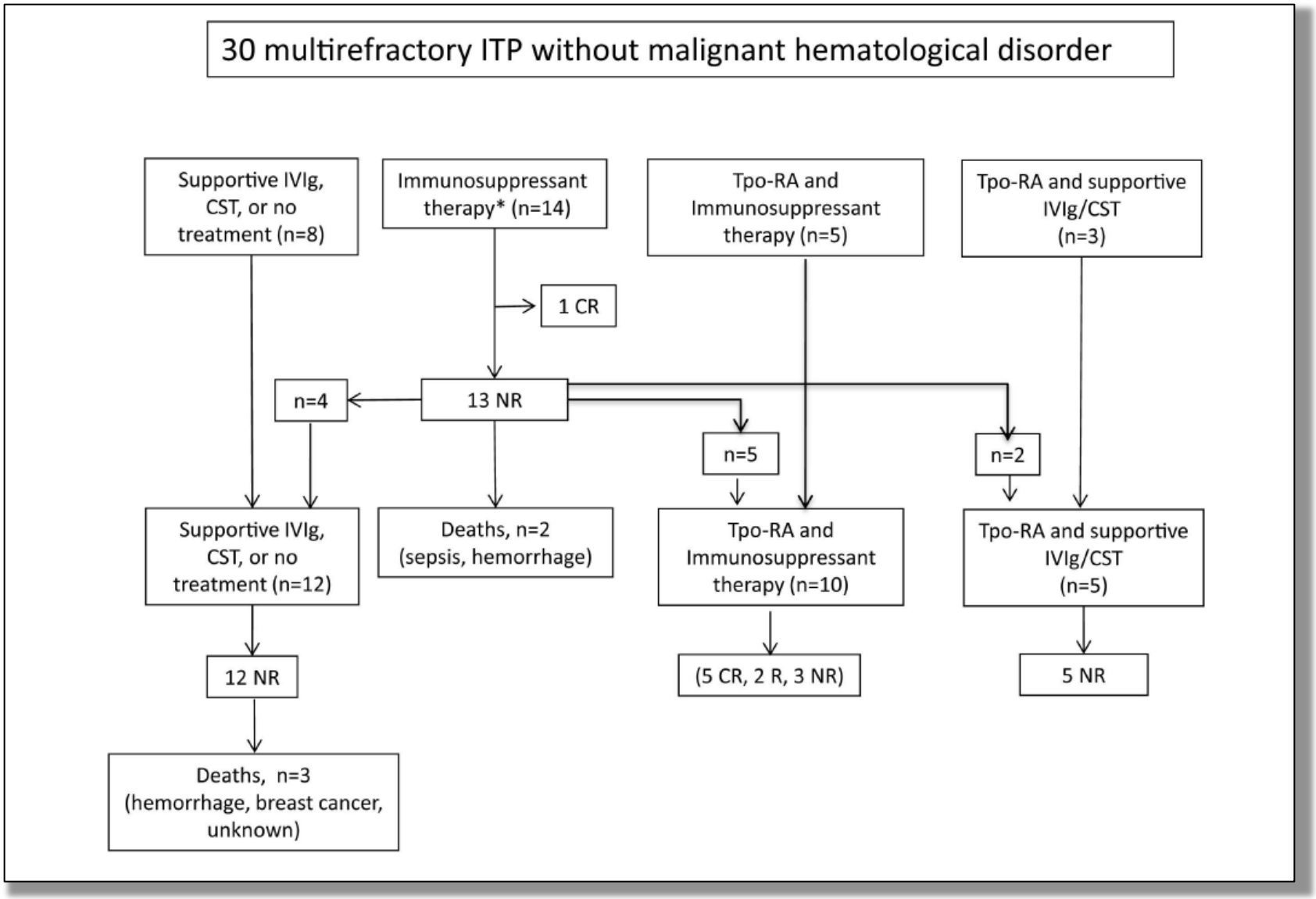
Ghanima et al, *Blood* 2012;120:960-969

Options as second-line treatment and choice **based on the following factors:**

Factors	Second line options			
	Splenectomy	**Rituximab ***	**TPO-RAs**	**Dapsone*, danazol***
Presence of Restriction on use of TPO-Ras /rituximab by health funding authorities	PROS	CONS	CONS	
Patient's and physician's preferences	PROS	PROS	PROS	PROS**
Newly diagnosed or persistent ITP (chronic <1 year)	CONS			
Presence of severe co-morbidities	CONS			
Elederly, Presence of severe cognitive impairment			Use Romiplostim in priority for a better compliance	
Elderly, Poor life expectancy	CONS			
History of severe infection, hypogammaglobulinemia, previous prolonged treatment with steroids or immunosuppressive drugs	AVOID	AVOID	PROS	
History of thrombosis	AVOID	PROS	AVOID	AVOID for danatrol
Splenic destruction of platelet in isotopic study if available*	PROS			

- off-label use
- ** for patients with minor or no bleeding manifestations (avoid danazol in men with an history of prostate cancer)

Characteristics, outcome and response to therapy of multirefractory chronic immune thrombocytopenia



Mahévas M *et al. Blood.* 2016 Sep 22;128(12):1625-30

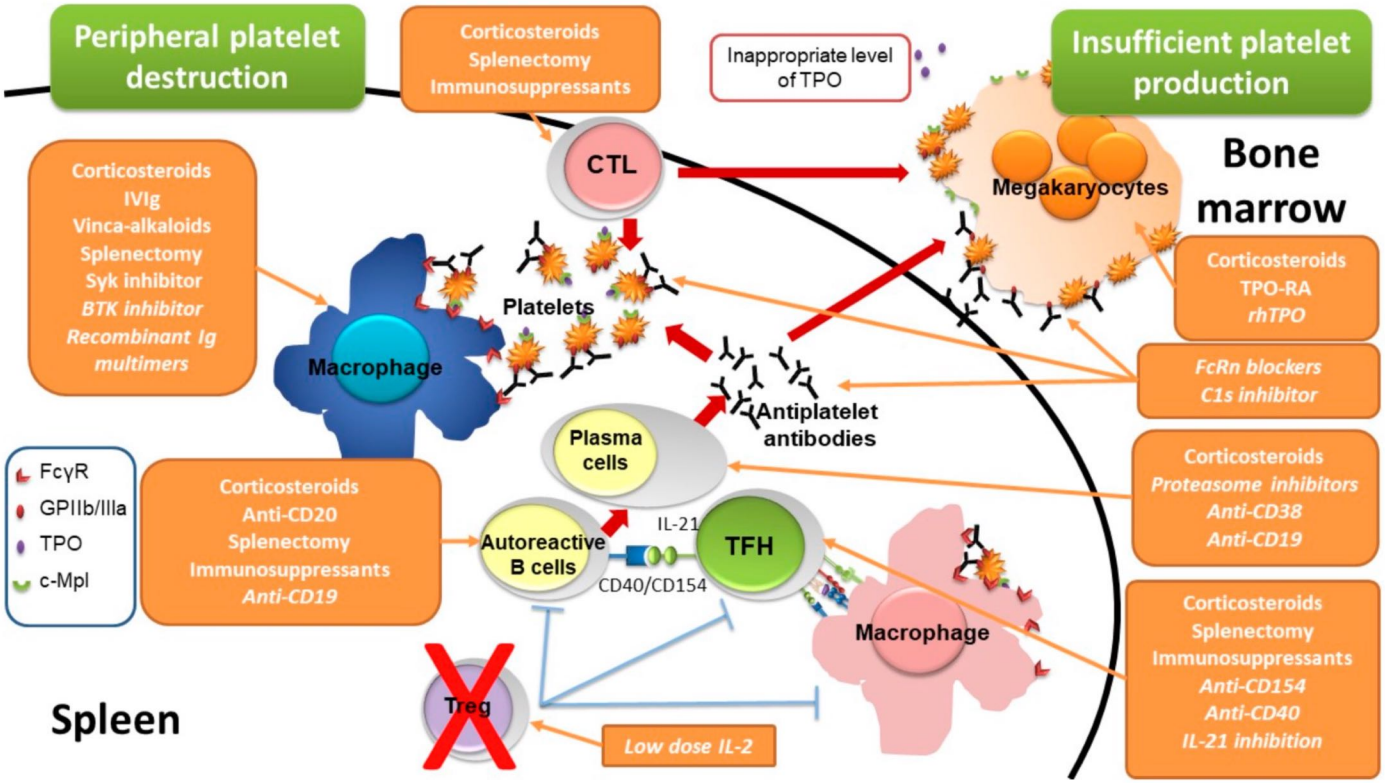


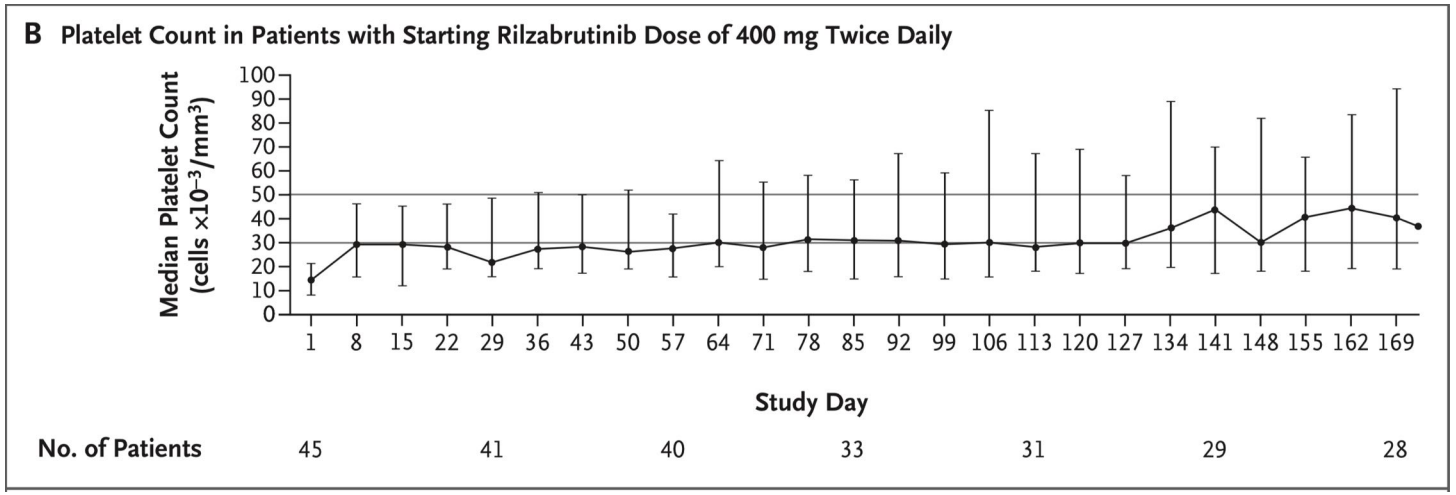
Figure 1. Pathogenesis of immune thrombocytopenia and sites of drug action. Immune thrombocytopenia results from both a peripheral destruction of platelets, mostly occurring in the spleen, and an insufficient bone marrow production. Peripheral platelet destruction is supported by antiplatelet antibodies produced by plasma cells that differentiate from B cells stimulated by T follicular helper cells through the CD40/CD154 axis and IL-21 production. Antiplatelet antibodies

Audia et al, *J. Clin. Med.* **2021**, *10*, 1004.

Rilzabrutinib, an oral BTK inhibitor, in immune thrombocytopenia

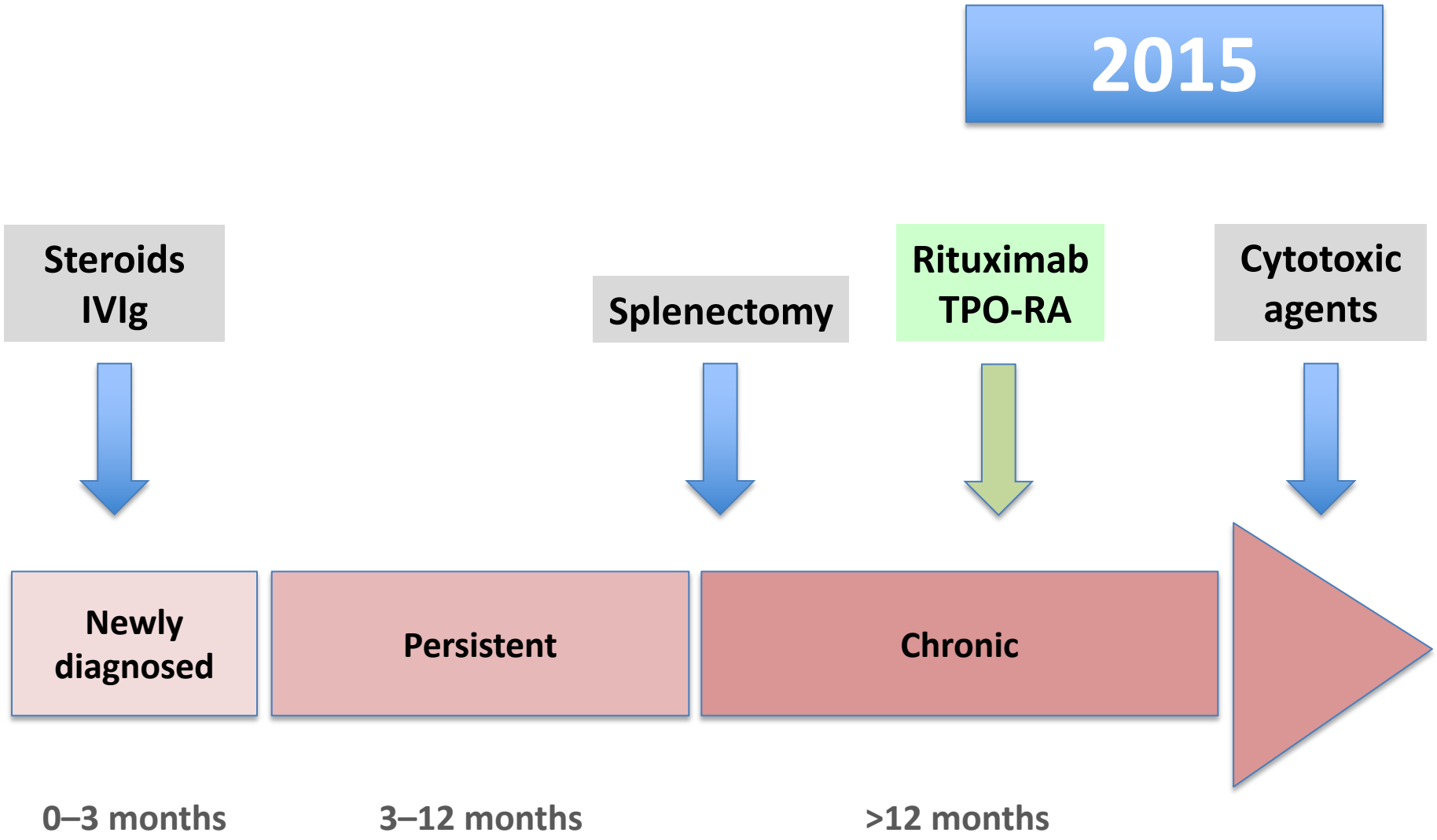
Kuter at al, *NEJM 2022; 386: 1421-31*.

- BTK: B-cell maturation, Ab production and Fc $gamma$ signaling
- Rilzabrutinib: BTK –
- Open study, dose escalating, 24weeks
- Median age 50 yrs (19-74)
- Platelet count 15 (2-33) G/L
- Median of 4 previous Tt (TPO-Ras 58%, rituximab 40%, splenectomy 25%
- Primary endpoint (plt > 50 G/L): 40%
- No grade 3 or 4 side effect



How has the way we treat ITP changed over the last decade?

Summary



IVIg, intravenous immunoglobulin.

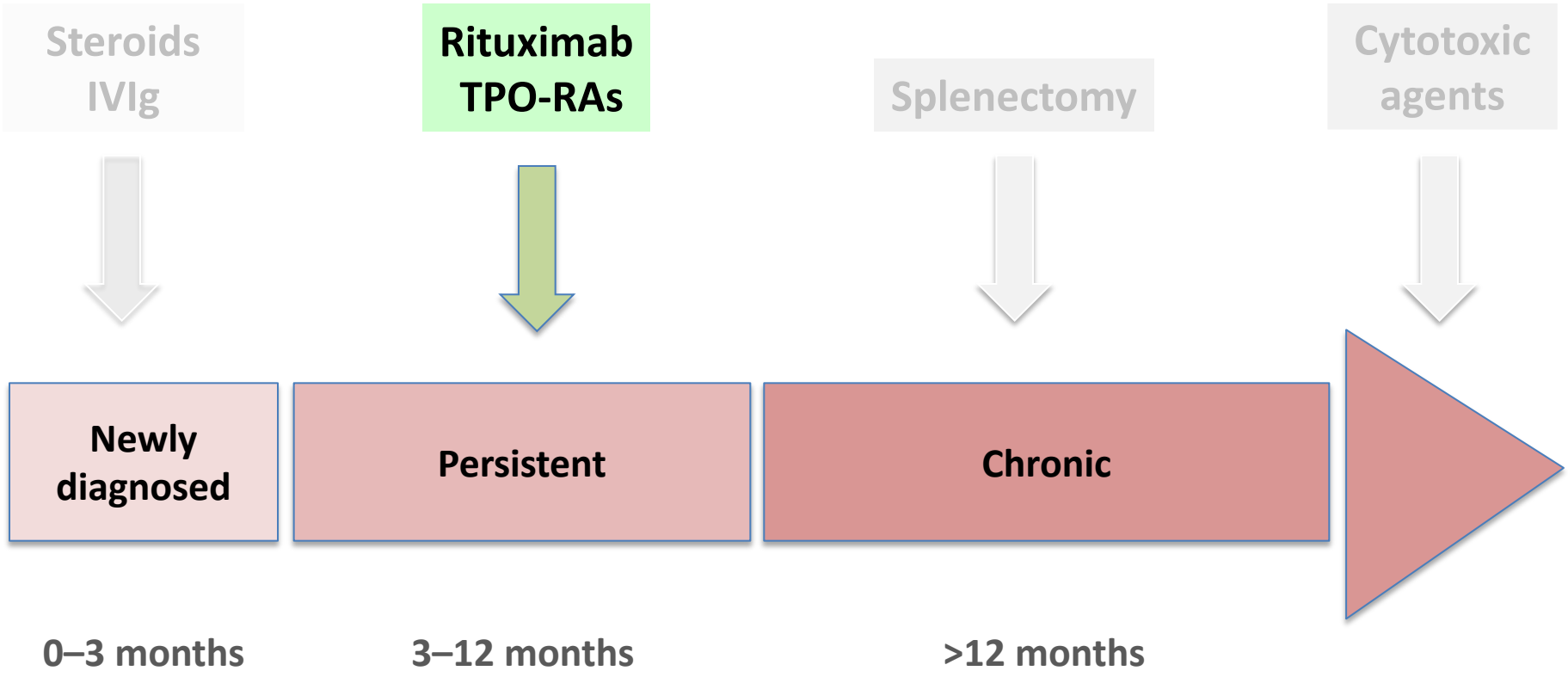
How has the way we treat ITP changed over the last decade?

Summary

Questions?

- Rituximab before TPO-RAs?
- TPO-RAs before rituximab?
- Transient treatment with TPO-RAs?
- Rituximab with dexamethasone?

2022



IVIg, intravenous immunoglobulin.

Prospective

- **Better knowledge of pathophysiology**

- **To determine pronostic factors**
  - -Chronicity
  - - Response to treatment