Place du Romiplostim dans prise en charge du PTI de l'adulte

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PR-NPL-DZA-000018-10-2017

Epidémiologie du PTI en France

- 3200 admissions d'adultes chaque année
- Parmi ces hospitalisations, 2/3 de PTI nouvellement diagnostiqués
- Age moyen au diagnostic: 55 ans (H≈F)
- Passage à la chronicité dans 67% des cas chez l'adulte
- 60 cas d'hémorragies intracérébrales/an avec une mortalité voisine de 50%

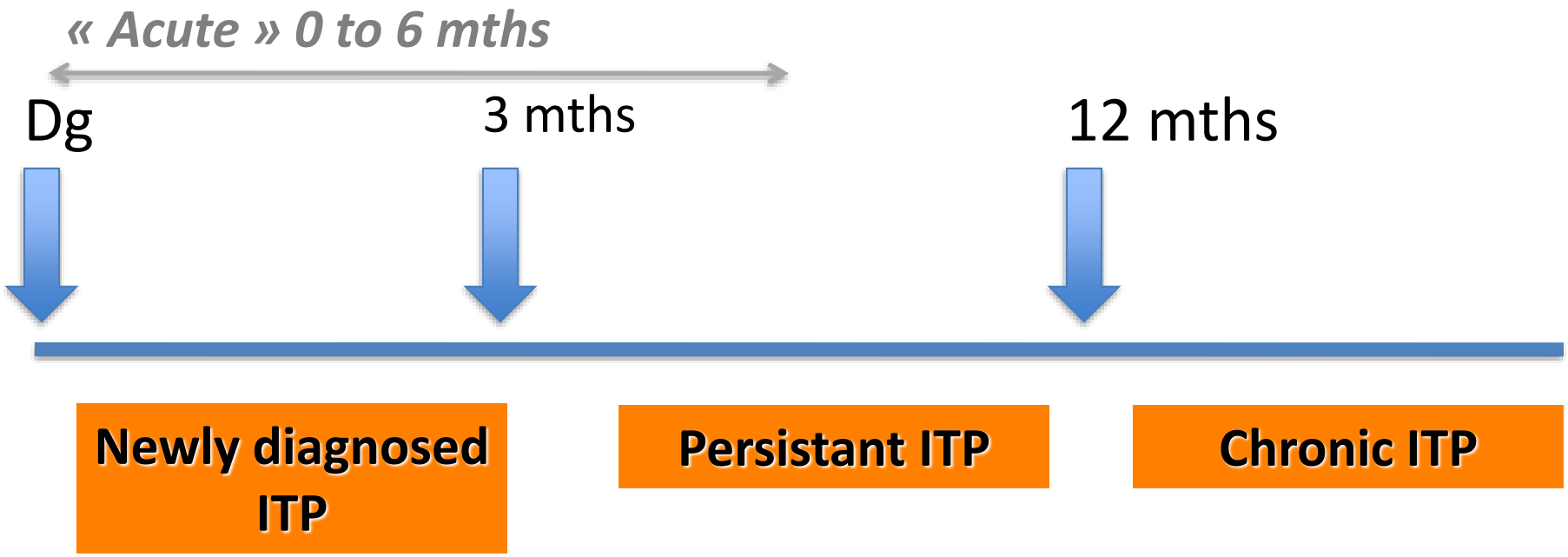
Michel et al, Br J Haematol 2015; 170: 218-22.
Moulis et al, Blood 2014; 124: 3308-15

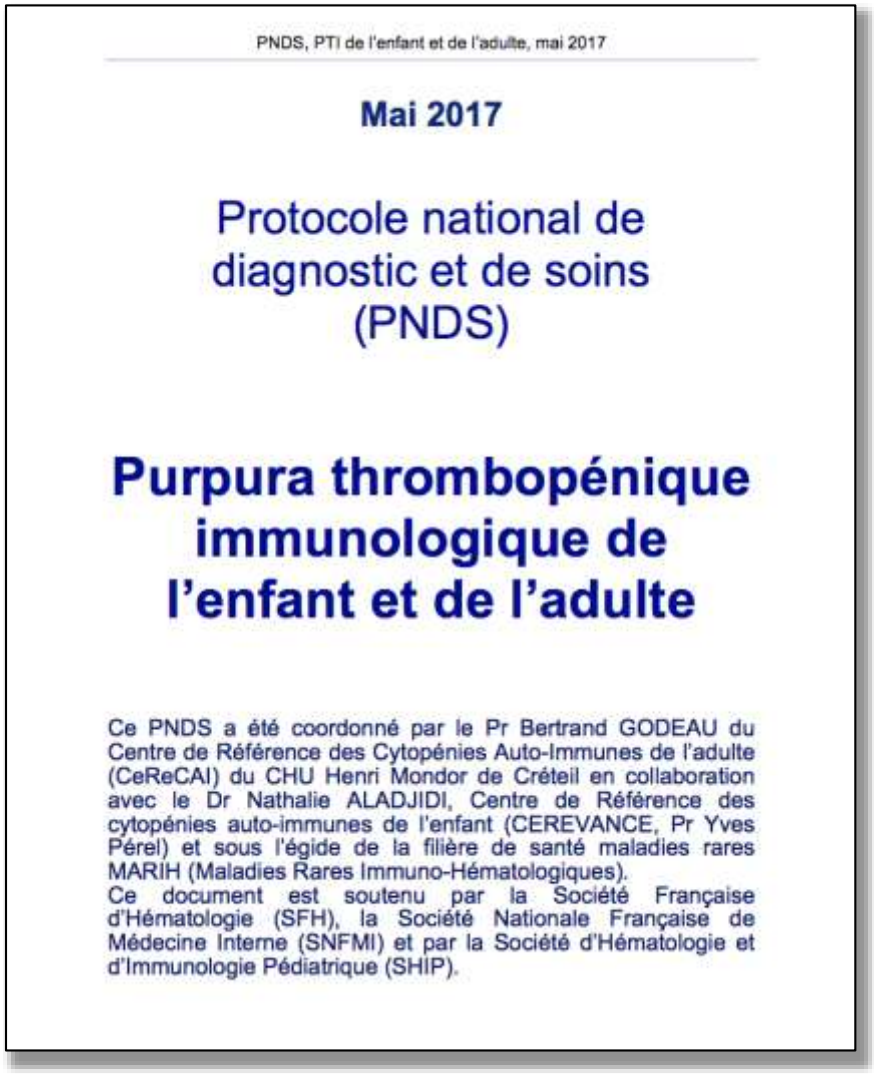
Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group

F Rodeghiero et al

BLOOD, 12 MARCH 2009; 113, 2386-93

ITP duration





https://www.has-sante.fr/.../**pnds-purpura-thrombopenique-immunologique**

Les traitements de première ligne

- **Prednisone**, 1mg/kg/j pendant 3 semaines puis arrêt rapide
- Ou **Dexamethasone**, 40mg/j pendant 4j
- **IgIV**: 1 à 2 g/kg réservées aux formes avec syndrome hémorragique grave
- **Transfusions de plaquettes** réservées aux formes avec mise en jeu du pronostic vital et en association avec les traitements précédents.

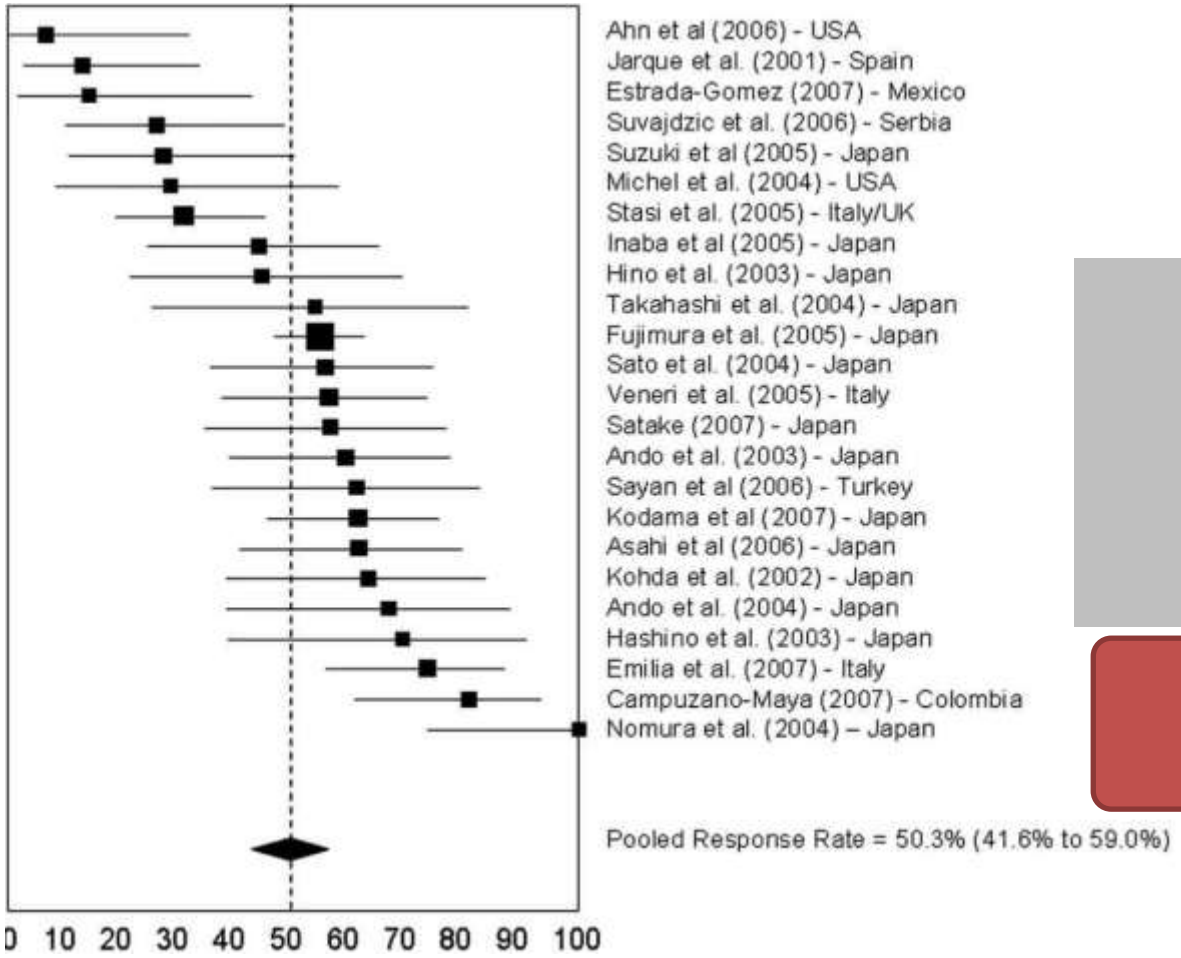
Les traitements de seconde ligne

- Pas de corticothérapie prolongée
- Eradication de l'Helicobacter Pylori
- **Disulone** (Dapsone®)
- **Rituximab** (Mabthéra®)
- **Agonistes du récepteur de la TPO**
  - Romiplostim (N Plate®)
  - Eltrombopag (Revolade®)
- **Immunosuppresseurs**
- **Splénectomie**

BLOOD, 2009; 113: 1231-40

Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review

Roberto Stasi,[1] Ameet Sarpatwari,[2] Jodi B. Segal,[3] John Osborn,[4] Maria Laura Evangelista,[1] Nichola Cooper,[5] Drew Provan,[6] Adrian Newland,[6] Sergio Amadori,[7] and James B. Bussel[8]



H. pylori and ITP

ORR: 50%

ORR, overall response rate.

Stasi R, *et al. Blood* 2009;113:1231–40.

Dapsone et PTI

POUR

- 30 à 50% de réponse
- Peu coûteux
- Bien toléré

CONTRE

- Risque cutané
- CI si déficit en G6PD
- Rechutes fréquentes à l'arrêt
- Pas d'AMM

Effet à long terme ?
Sécurité d'emploi ?

Rituximab PTI chronique

POUR

- > 50% de réponse initiale
- Efficace chez le splénectomisé
- *Nouvelle cure efficace*
- Facile à administrer
- Doses faibles efficaces
- 2 injections fixes de 1g aussi efficaces que le schéma « classique » du lymphome
- Tolérance satisfaisante

CONTRE

- Efficacité à long terme décevante (25%)
- Pas d'AMM

Mycophenolate mofetil (MMF) therapy for severe immune thrombocytopenia

Taylor A, et al. *Br J Haematol* 2015;171:625–30

Response of primary and secondary ITP patients to MMF

	Complete response	Response	No response
Primary ITP			
Total number of patients (29)	11	4	14
Number of previous lines of therapy (mean)	2.3	2	3.4
Time from diagnosis to MMF (mean, months)	60.8	163	31.3
Secondary ITP			
Total number of patients (17)	4	5	8
Number of previous lines of therapy (average)	4.3	3	2.8
Time from diagnosis to MMF (average, months)	68.8	73.4	21.5

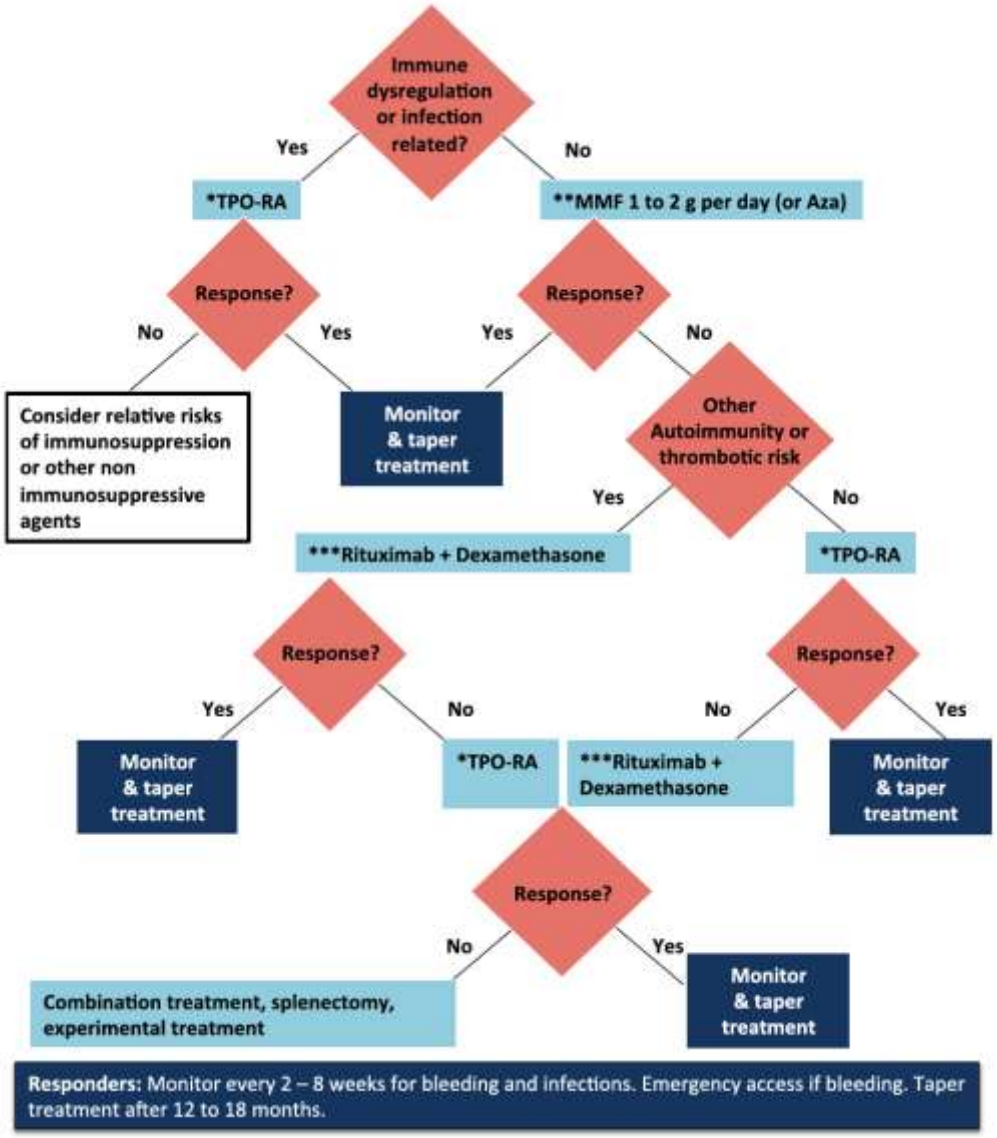
Overall response rate: 52%

Taylor A, et al. Br J Haematol 2015;171:625–30

State of the art – how I manage immune thrombocytopenia

Nichola Cooper

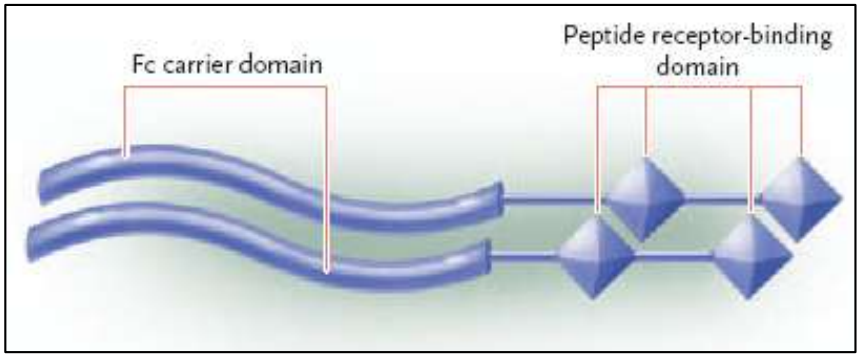
British Journal of Haematology, 2017, **177,** 39–54



TPO-r agonistes

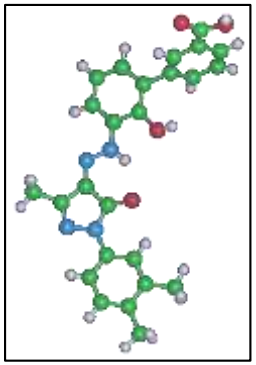
Romiplostim (Amgen®)

AMG 531



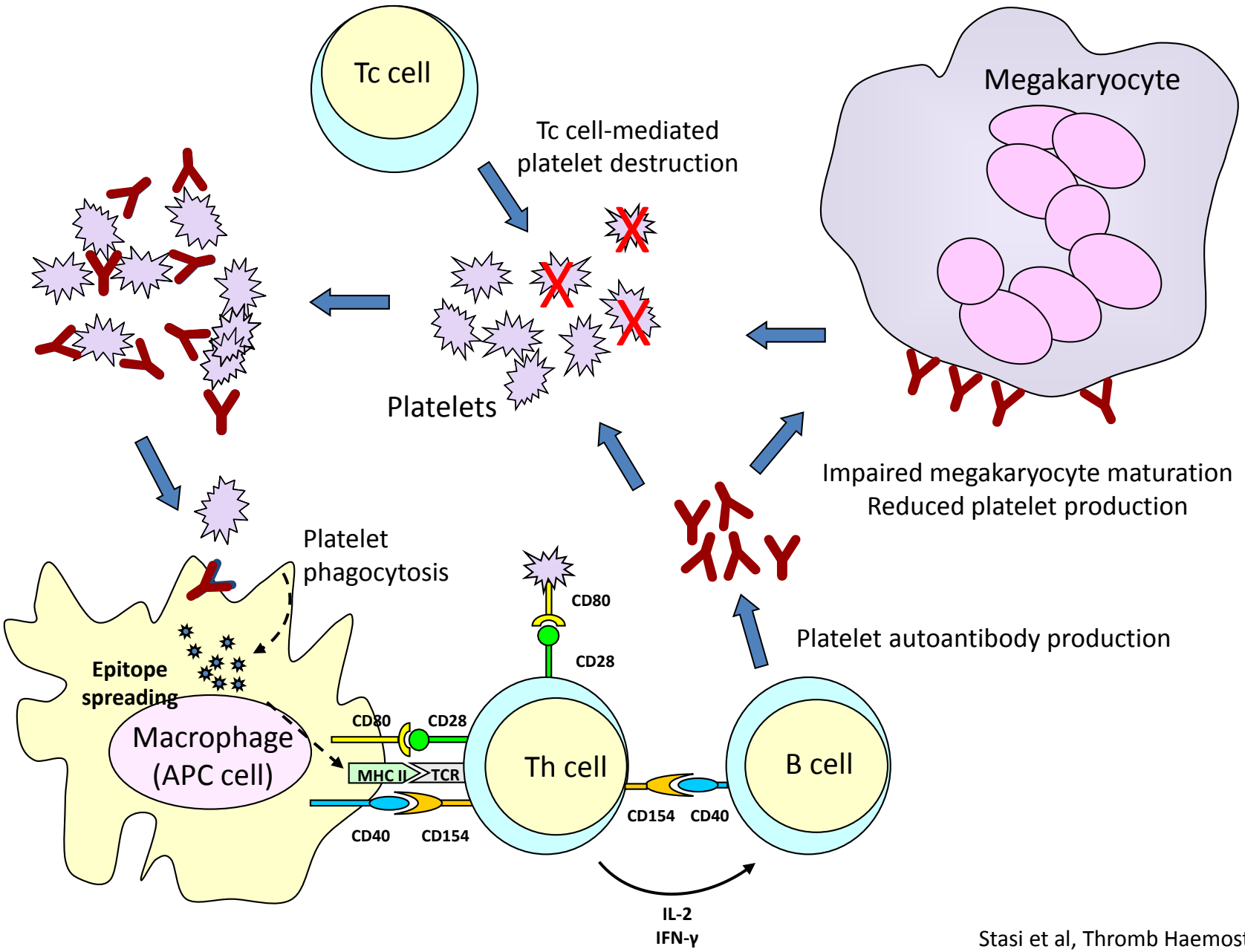
Partie Fc ↑ la demi-vie de la molécule
Voie sous-cutanée 1 fois par semaine
Dosage 1 µg/kg à 10 µg/kg

Eltrombopag (Novartis®)



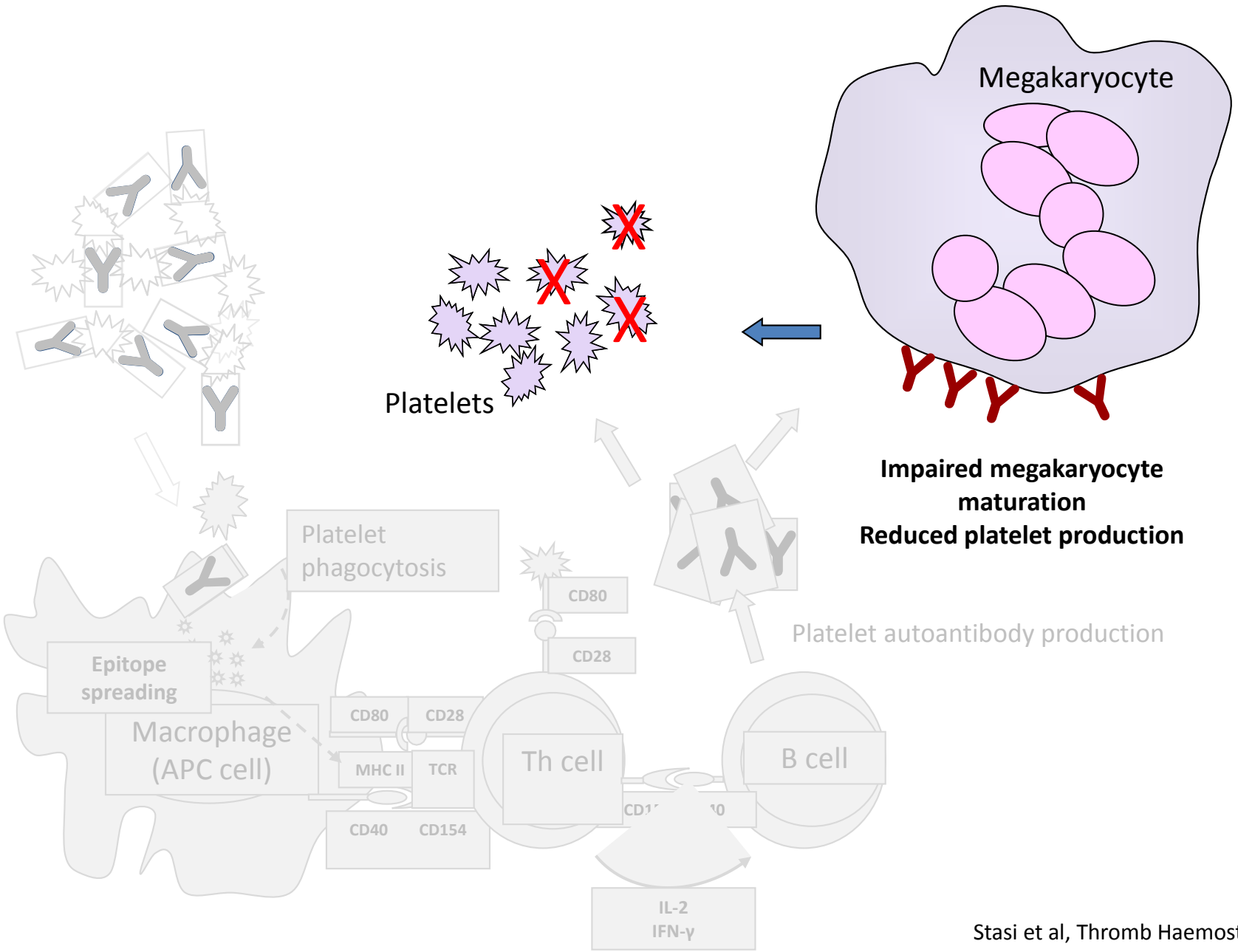
Voie orale quotidienne
Dosage 50 ou 75 mg

ITP Pathogenesis



Stasi et al, Thromb Haemostas. 2008

ITP Pathogenesis



Stasi et al, Thromb Haemostas. 2008

Romiplostim 1ers essais

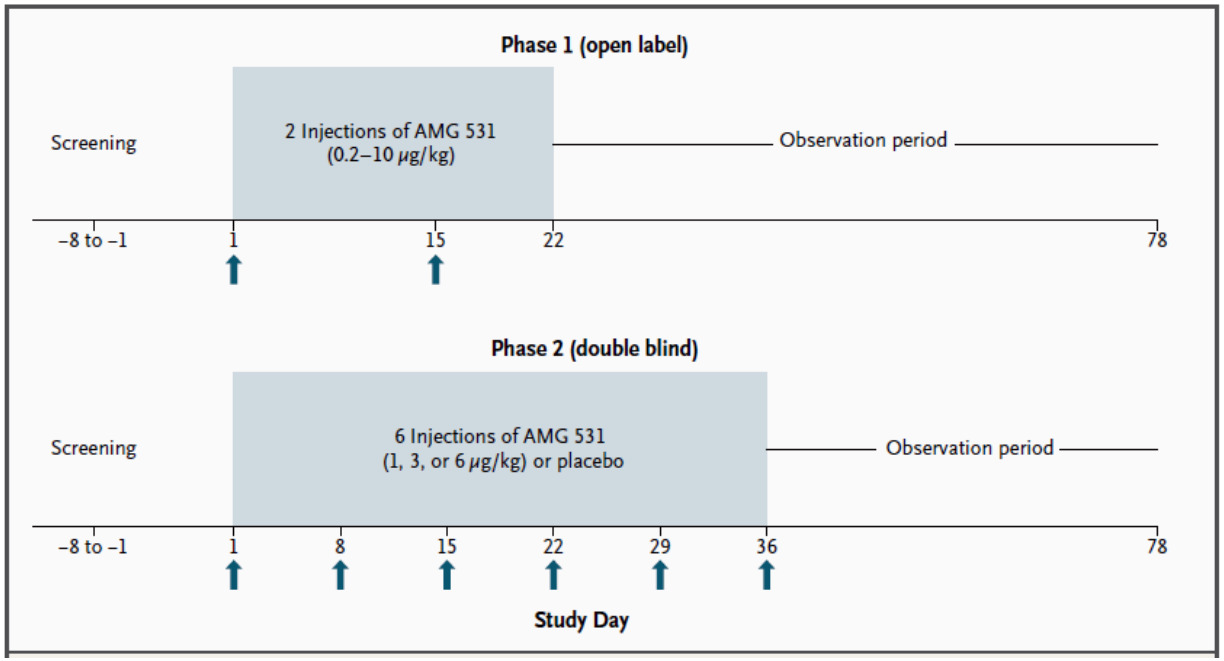
24 PTI >6mois
[Plaq]<20G/L
Splénectomie 90%
2 ou 6 injections par semaine

1
3
6
10
} µg/kg/sem

The NEW ENGLAND JOURNAL of MEDICINE
2006; 335: 1672-81

ORIGINAL ARTICLE

AMG 531, a Thrombopoiesis-Stimulating Protein, for Chronic ITP



BUSSEL J, N Engl J Med 355;16, 2006

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

Kuter *et al*, **Lancet**. 2008;371(9610):395-403.

Methods

In two parallel trials, 63 splenectomised and 62 non-splenectomised patients with ITP and a mean of three platelet counts 30×109/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.

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

David J Kuter, James B Bussel, Roger M Lyons, Vinod Pullarkat, Terry B Gernsheimer, Francis M Senecoff, Louis M Aledort, James N George, Craig M Kessler, Miguel A Sanz, Howard A Liebman, Frank T Slweck, J Th M de Wolf, Emmanuelle Bourgeois, Troy H Guthrie Jr, Adrian Newland, Jeffrey S Warner, Solomon I Hamburg, Carlos Grande, François Lefrère, Alan EE Lichtin, Michael D Tarantino, Howard R Terebelo, Jean-François Viallard, Francis J Cuenco, Ronald S Go, David H Henry, Robert L Redner, Lawrence Rice, Martin R Schipperus, D Matthew Guo, Janet L Nichol

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 30×10⁹/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 50×10⁹/L to 200×10⁹/L. The primary objectives were to assess the efficacy of romiplostim as measured by a durable platelet response (platelet count ≥50×10⁹/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 NCT00103336.

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 50×10⁹/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.

Introduction

Chronic immune thrombocytopenic purpura (ITP) is an autoimmune disorder that is characterised predominantly by antibody-mediated platelet destruction.[1,2] Available therapies—such as corticosteroids, intravenous immunoglobulins, splenectomy, rituximab, and cyclophosphamide—primarily focus on reduction of this platelet destruction.[3,4] However, recent evidence suggests that decreased platelet production might also have a role in ITP.[5,6] For example, kinetic studies have shown that platelet production is not increased (contrary to expectations) in over three-quarters of thrombocytopenic patients with chronic ITP,[7,8] and thrombopoietin concentrations are normal or near normal in patients with this disease.[9–11] Moreover, antiplatelet antibodies inhibit in-vitro growth of megakaryocyte precursor cells,[5,6] and bone marrow megakaryocytes in ITP can be apoptotic.[12] Often, therapies aimed at reduction of platelet destruction are either ineffective or poorly tolerated. Therefore, treatments aimed at increasing platelet production, alone or in combination with existing therapies, provide an opportunity to improve outcomes in patients with this chronic disease.

Romiplostim (formerly know as AMG531) is a novel thrombopoiesis stimulating protein (peptibody) that binds to and activates the human thrombopoietin receptor despite having no sequence homology with human thrombopoietin.[13,14] Romiplostim produces a

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

Kuter *et al*, **Lancet**. 2008;371(9610):395-403.

The overall platelet response rate was noted in 88% of non-splenectomised and 79% of splenectomised patients given romiplostim compared with 14% of patients given placebo ($p<0{\cdot}0001$).

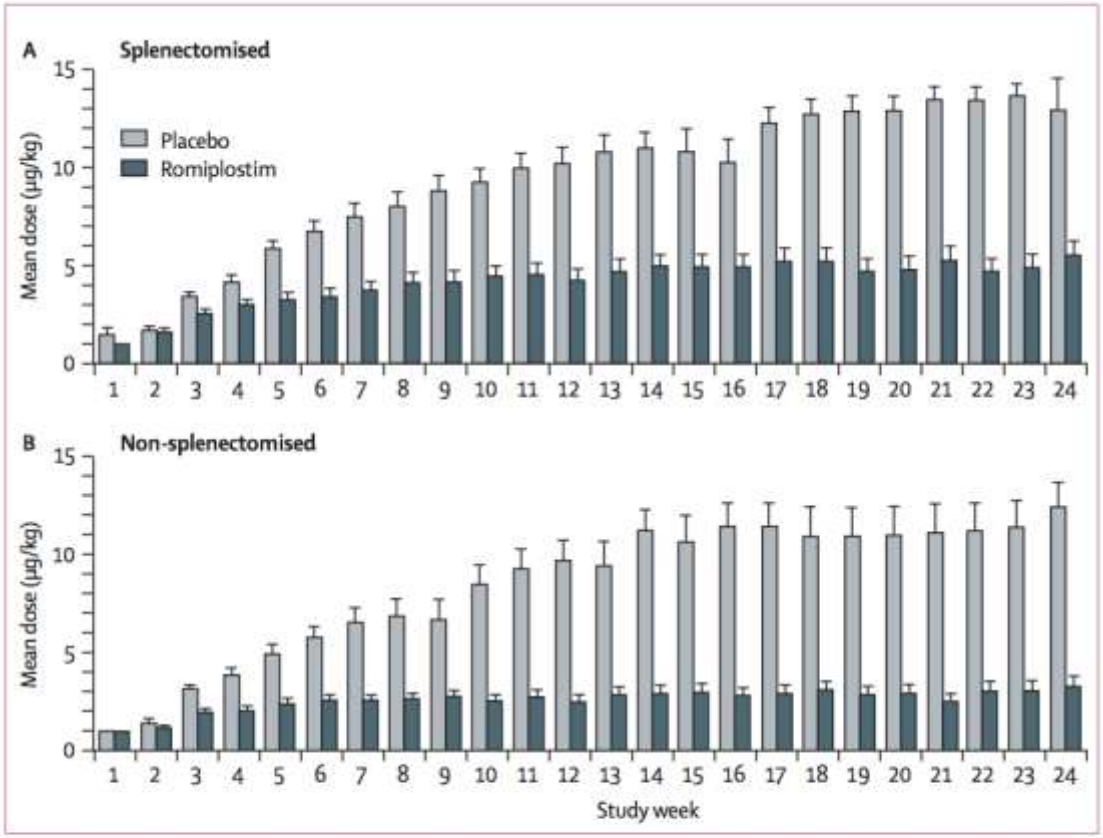


***Figure 2*: Mean dose of romiplostim or placebo per week at every study visit for splenectomised (A) and non-splenectomised (B) patients**

Error bars show SEM. Throughout the 24-week study period, the median dose of romiplostim needed to maintain target platelet counts of 50×10^9/L to 200×10^9/L was roughly 3 µg/kg in splenectomised patients and 2 µg/kg in non-splenectomised patients.

Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial

Articles

Lancet 2009; 373: 641–48

James B Bussel, Drew Provan, Tahir Shamsi, Gregory Cheng, Bethan Psaila, Lidia Kovaleva, Abdulgabar Salama, Julian M Jenkins, Debasish Roychowdhury, Bhabita Mayer, Nicole Stone, Michael Arning

Sustained response

65 % of cases

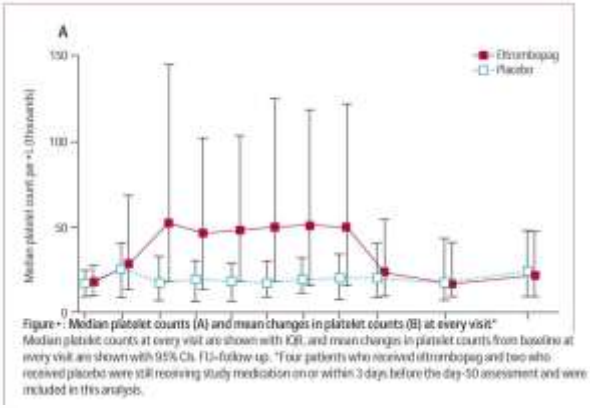


Figure •: Median platelet counts (A) and mean changes in platelet counts (B) at every visit.* Median platelet counts at every visit are shown with IQR, and mean changes in platelet counts from baseline at every visit are shown with 95% CIs. FU=follow-up. *Four patients who received eltrombopag and two who received placebo were still receiving study medication on or within 3 days before the day-50 assessment and were included in this analysis.

BLOOD 2009; 113: 2161-71

Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP

James B. Bussel,[1] David J. Kuter,[2] Vinod Pullarkat,[3] Roger M. Lyons,[4] Matthew Guo,[5] and Janet L. Nichol[5]

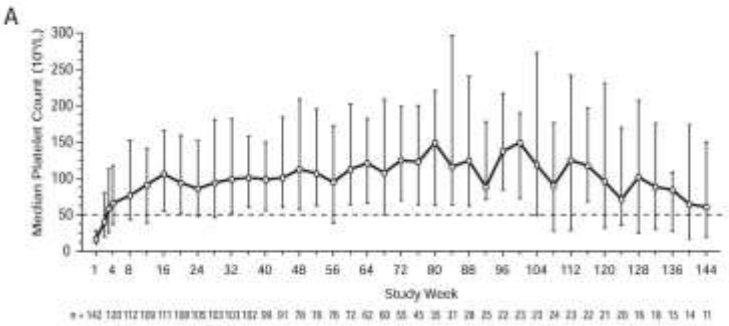


Figure 2. Platelet counts and platelet responses by study week. (A) Median (25th [Q1] and 75th [Q3] percentiles) platelet counts by study week. Median platelet counts increased sharply during the first 4 weeks of treatment and then more gradually through week 16. (B) Percentage of patients with a platelet response over time. A platelet response was defined as a platelet count of 50 • 10^9/L or more that was at least double the platelet count at baseline in the absence of rescue medication within the preceding 8 weeks. After 1 dose, 30% of patients achieved a platelet response, and after 3 doses, 51% achieved a response. Over the course of the study, a platelet response was observed in 87% of all patients.

Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a romiplostim compassionate-use program.
Khellaf et al, Blood. 2011 Oct 20;118(16):4338-45.

Et dans la vraie vie ?

Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a romiplostim compassionate-use program

Mehdi Khellaf,[1] Marc Michel,[1] Philippe Quittet,[2] Jean-François Viallard,[3] Magda Alexis,[4] Françoise Roudot-Thoraval,[5] Stéphane Cheze,[6] Jean-Marc Durand,[7] François Lefrère,[8] Lionel Galicier,[9] Olivier Lambotte,[10] Gérard Panelatti,[11] Borhane Slama,[12] Gandhi Damaj,[13] Gérard Sebahoun,[14] Emmanuel Gyan,[15] Xavier Delbrel,[16] Nathalie Dhedin,[17] Bruno Royer,[18] Nicolas Schleinitz,[19] Jean-François Rossi,[2] Matthieu Mahévas,[1] Laetitia Languille,[1] Philippe Bierling,[20] and Bertrand Godeau[1]

[1]Department of Internal Medicine, Centre Hospitalier Universitaire (CHU) Henri-Mondor, Assistance Publique–Hôpitaux de Paris (AP-HP), Université Paris Est Créteil, Créteil, France; [2]Department of Hematology, CHU Lapeyronie, Montpellier, France; [3]Department of Infectious Diseases, CHU Haut-Lévêque, Pessac, France; [4]Department of Hematology, CHU la Source, Orléans, France; [5]Department of Public Health, Université Paris Est Créteil, Créteil, France; [6]Groupe Francophone des Myélodysplasies, Caen, France; [7]Department of Internal Medicine, Hôpital de la Conception, Assistance Publique–Hopitaux de Marseille (AP-HM), Marseille, France; [8]Department of Hematology, CHU Necker, AP-HP, Paris, France; [9]Department of Hematology, CHU Saint-Louis, AP-HP, Paris, France; [10]Department of Internal Medicine, CHU Bicêtre, AP-HP, Kremlin-Bicêtre, France; [11]Department of Hematology, CHU Fort de France, Fort de France, France; [12]Department of Hematology, Centre Hospitalier (CH) d'Avignon, Avignon, France; [13]Department of Hematology, CHU d'Amiens, Amiens, France; [14]Department of Hematology, CHU Hôpital Nord, AP-HM, Marseille, France; [15]Department of Hematology, CHU de Tours, Tours, France; [16]Department of Rhumatology, CH de Pau, Pau, France; [17]Department of Hematology, CHU Hôpital Pitié-Salpêtrière, AP-HP, Paris, France; [18]Department of Hematology, CHU Hôpital Sud, Amiens, France; [19]Department of Internal Medicine, Hôpital de la Conception, AP-HM, Marseille, France; and [20]Établissement Français du Sang, CHU Henri-Mondor, AP-HP, Creteil, France

Romiplostim, a thrombopoietic agent with demonstrated efficacy against immune thrombocytopenia (ITP) in prospective controlled studies, was recently licensed for adults with chronic ITP. Only France has allowed romiplostim compassionate use since January 2008. ITP patients could receive romiplostim when they failed to respond to successive corticosteroids, intravenous immunoglobulins, rituximab, and splenectomy, or when splenectomy was not indicated. We included the first 80 patients enrolled in this program with at least 2 years of follow-up. Primary platelet response (platelet count ≥ 50 × 10⁹/L and double baseline) was observed in 74% of all patients. Long-term responses (2 years) were observed in 47 (65%) patients, 37 (79%) had sustained platelet responses with a median platelet count of 105 × 10⁹/L (interquartile range, 75-167 × 10⁹/L), and 10 (21%) were still taking romiplostim, despite a median platelet count of 38 × 10⁹/L (interquartile range, 35-44 × 10⁹/L), but with clinical benefit (lower dose and/or fewer concomitant treatment(s) and/or diminished bleeding signs). A high bleeding score and use of concomitant ITP therapy were baseline factors predicting romiplostim failure. The most frequently reported adverse events were: arthralgias (26%), fatigue (13%), and nausea (7%). Our results confirmed that romiplostim use in clinical practice is effective and safe for severe chronic ITP. This trial was registered at www.clinicaltrials.gov as #NCT01013181. (*Blood*. 2011;118(16):4338-4345)

Introduction

Immune thrombocytopenia (ITP) in adults is a chronic autoimmune disorder characterized by low platelet counts and mucocutaneous bleeding.[1-5] ITP signs and symptoms vary widely. Some patients have no symptoms or minimal bruising, whereas others experience severe bleeding. Whereas ITP in children is usually a self-limited disease that spontaneously disappears within few weeks, ~ 70% of adults remain thrombocytopenic after 1 year and, hence, have chronic ITP. The overall prognosis of ITP is good, with < 2% mortality, but the latter can rise to 10% for a subgroup of patients with chronic severe ITP refractory to splenectomy.

ITP has long been considered to be only a matter of accelerated platelet destruction, and most of the currently available therapies increase platelet counts, mainly by slowing the platelet destruction rate. However, some evidence shows that ITP is also a matter of impaired platelet production.[6,7] Suboptimal platelet production and relatively low thrombopoietin levels in ITP patients would be consistent with an important role for thrombopoietic agents in ITP management.

Romiplostim is a peptibody that was the first thrombopoietic agent developed for this indication.[8] It has been reported to be a highly effective treatment for both splenectomized and nonsplenectomized patients in pivotal clinical studies[9-12] and has been accorded Food and Drug Administration approval for the treatment of ITP patients in the United States, after failure of a first-line therapy (either corticosteroids or intravenous immunoglobulins [IVIg]). More recently, romiplostim was licensed in Europe after splenectomy failure or contraindication. Although romiplostim has been available in the United States since January 2009, no data on

Submitted March 1, 2011; accepted July 14, 2011. Prepublished online as *Blood* First Edition paper, August 10, 2011; DOI 10.1182/blood-2011-03-340166.

An inside *Blood* analysis of this article appears at the front of this issue.

The online version of this article contains a data supplement.

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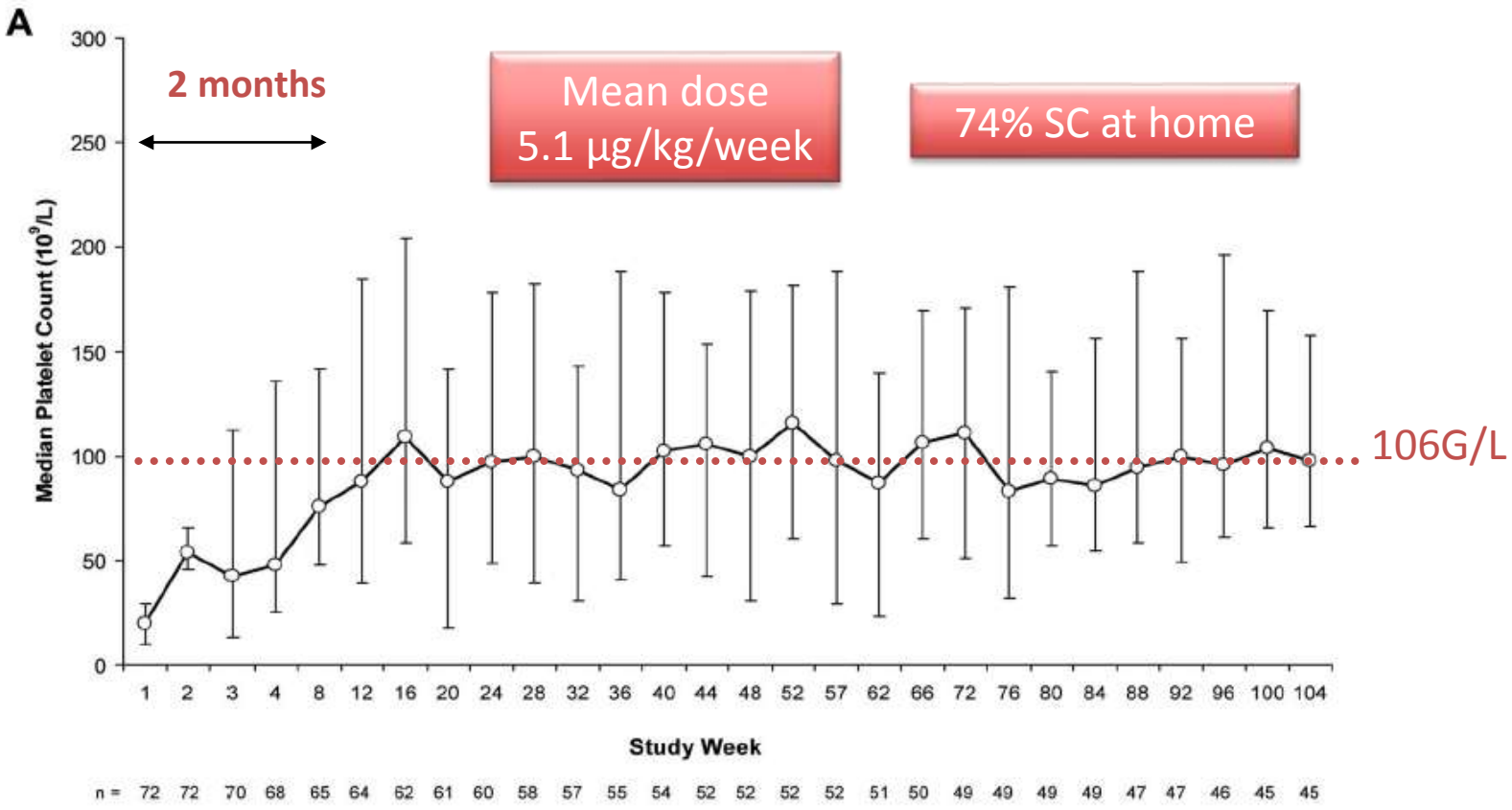
Khellaf et al, Blood. 2011 Oct 20;118(16):4338-45.



TPO-r agonistes et PTI

eltrombopag (Revolade®), romiplostim (Nplate®)

POUR

- EBM
- Réponse dans 70% des cas
- Efficaces si splénectomie
- Efficace en préparation à la splénectomie
- Réponse soutenue
- Bien tolérés à court terme
- AMM
- Switch possible en l'absence de réponse avec l'un des 2 agonistes disponibles

CONTRE

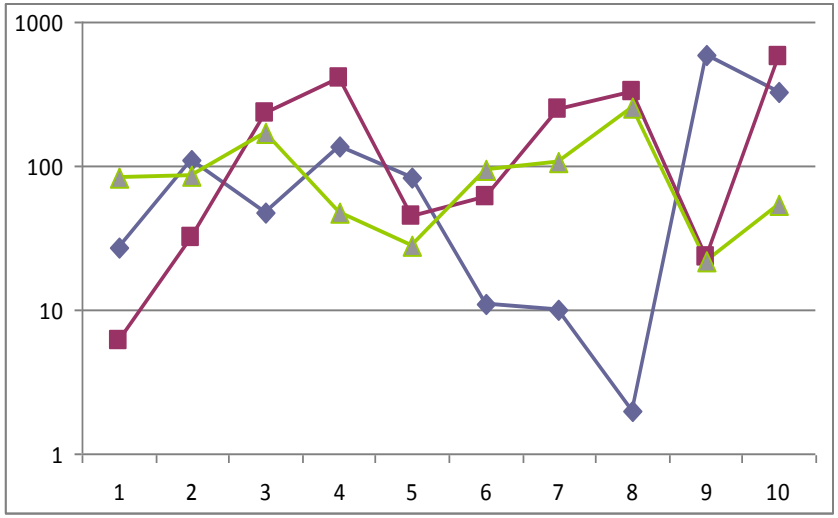
- Effet suspensif
- Rebond à l'arrêt
- Sécurité à long terme inconnue
- Coût

Questions non résolues

- Causes des échecs
- Réponse à long terme possible ?

Platelet fluctuation and TPO-r mimetics
Why ?

Log Plaq G/L



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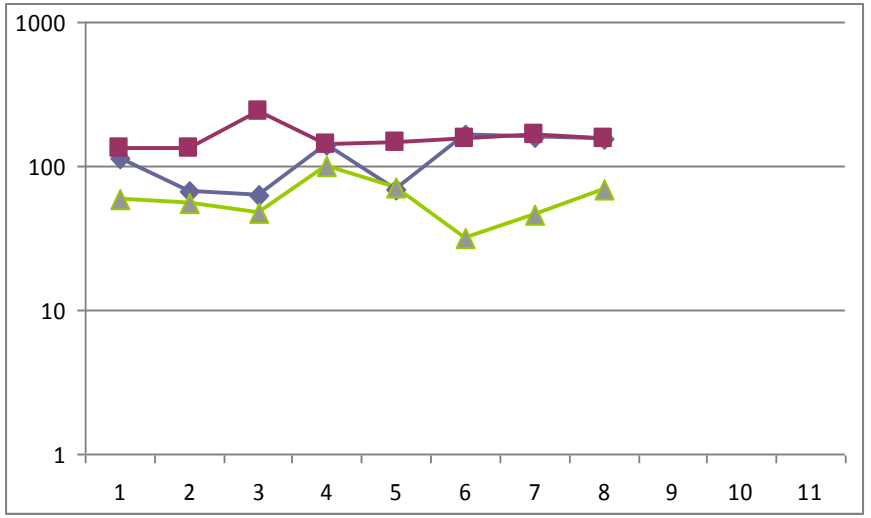


TPO-r mimetic n°1 → **TPO-r mimetics n°2**

Khellaf et al, Haematologica 2013

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

ARTICLES

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

bjh research paper

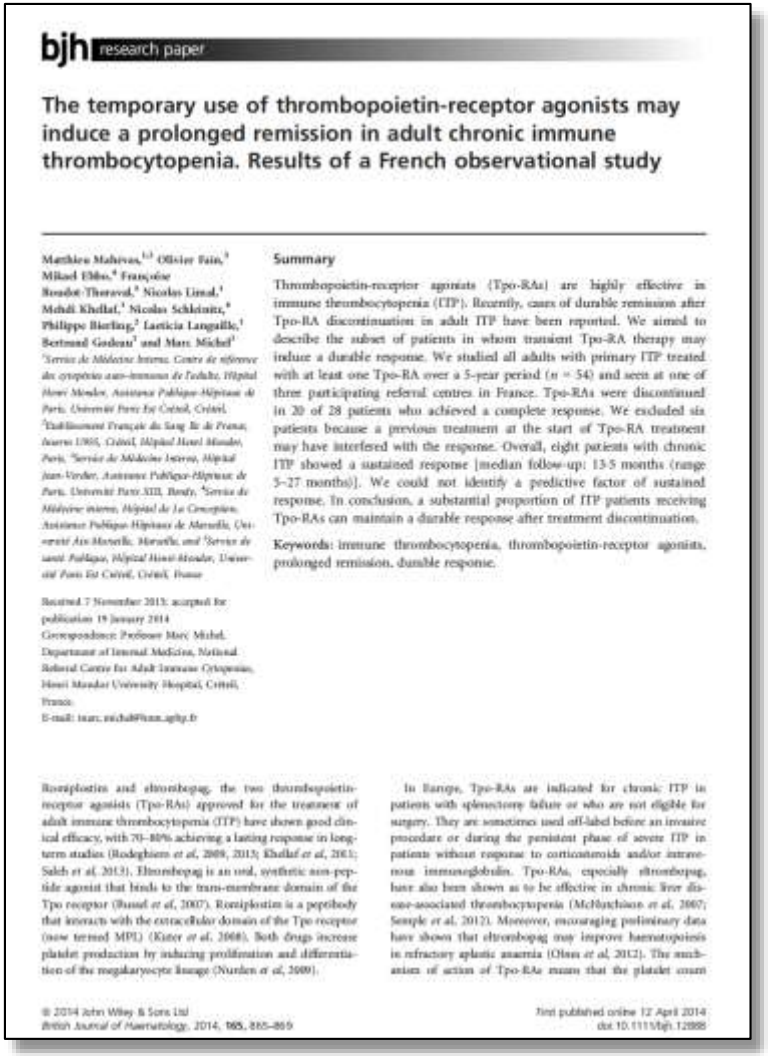
Use of eltrombopag after romiplostim in primary immune thrombocytopenia

ORIGINAL ARTICLE

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

The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study
Mahévas *et al*, *Br J Haematol* 2014; 165: 865-9

- Observational study
- 54 patients treated with TPO-r+
- TPO-r+ discontinued in 20 complete responders
- **Sustained response in 8 evaluable patients** (median fu 13 mths, range 5-27)
- No predictive factor of sustained response



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*, 2013; 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; Sample *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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TPO-mimétiques et thrombose
Situations à risque?

- **Lupus, SAPL → <u>Risque de thrombose si APL+++</u>**
- **ATCD de thrombose**
- **Sujets âgés**
  - Romiplostim
  - Eltrombopag

] **Risque ± 10%**

Michel et al, *Ann Hematol* **94**,1973-1980 .
Olney et al, *ASH Annual Meeting Abstracts*, **118**: Abstract 3294

TPO mimetiques en pratique….

- Utilisable pendant la grossesse? **NON**
- Utilisable si insuffisance rénale? **OUI**
- Utilisable si hépatopathie? **ATTENTION (thrombose porte)**
- Comment les arrêter: **PROGRESSIVEMENT**
- Que faire si ATCD de thrombose: **NON (+/-)**
- Bonne option pour Lupus et SAPL: **NON (+/-)**
- Bonne option pour les urgences: **OUI et NON**
- Bonne option en gériatrie: **Pourquoi pas**

Romiplostim (N Plate®) Indications

- *Nplate® est indiqué chez l'adulte splénectomisé présentant un PTI chronique, réfractaire aux autres traitements (par exemple corticoïdes, immunoglobulines).*
- *Nplate® peut être envisagé comme traitement de seconde intention chez l'adulte non splénectomisé quand la chirurgie est contre-indiquée*

Ne pas oublier la splénectomie !

- Expérience!
- Efficace
- Sûre et possibilité de prévenir les complications
- Ne modifie pas la réponse aux Tt médicaux
- Possibilité de prédire la réponse (épreuves isotopiques)
- Peu coûteux
- Grossesse
- Respect des recommandations

Mais…

Complications de la splénectomie

- **Infection +++**
- Tumeur ?
- **Complications vasculaires**
  - Athérome ?
  - **Thromboses veineuses +**
  - **Thromboses arterielles +**
  - Evènements cardio-vasculaires
  - HTAP ?

Vascular complications after splenectomy for hematologic disorders

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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,[1] although splenectomy for trauma is becoming less common than in years past, resulting from more conservative nonoperative management of splenic injury.[3] 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.

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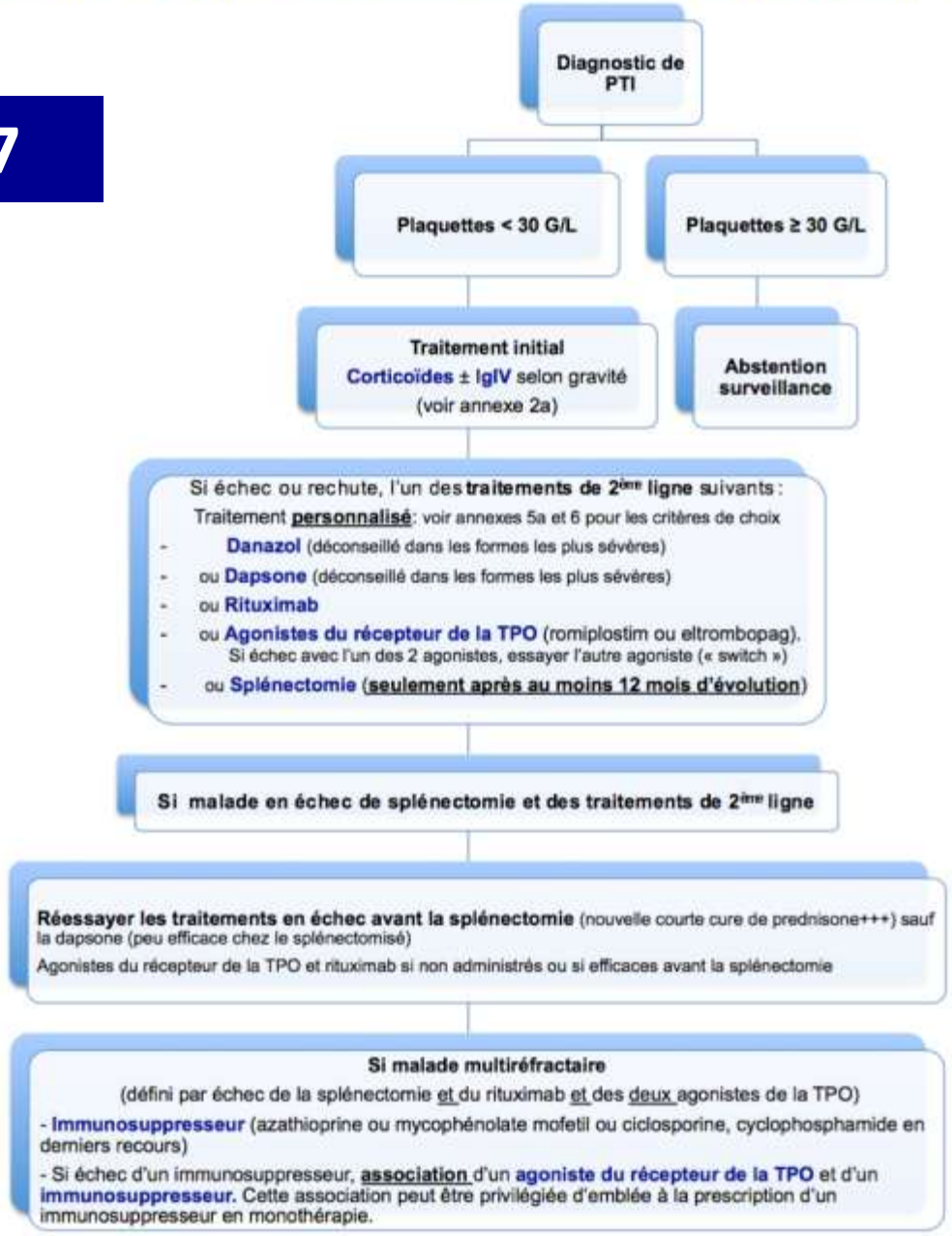
Annexe 4a.
Résumé de la stratégie thérapeutique au cours du PTI de l'adulte



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Annexe 6.
Critères pouvant être pris en compte pour le choix du traitement de seconde ligne au cours du PTI de l'adulte

Facteurs pouvant être pris en compte dans le choix du traitement de seconde ligne	Traitements de seconde ligne			
	Splénectomie	Rituximab	Agonistes du récepteur de la TPO	Dapsone ou Danazol
Avis et préférence du patient	OUI	OUI	OUI	OUI
PTI ayant une durée d'évolution ≤ 1 an	NON			
Co-morbidité(s) sévère(s)	NON		OUI	
Patient très âgé	NON			
Troubles cognitifs si patient âgé			Préférer le romiplostim à l'eltrombopag	
Espérance de vie limitée	NON		OUI	
Antécédents d'infection sévère, hypogammaglobulinémie, exposition antérieure à une corticothérapie prolongée ou des immunosuppresseurs	À EVITER	À EVITER	OUI	
Antécédents ou facteurs de risque de thromboses veineuses et/ou artérielles	À EVITER	OUI	À EVITER	À EVITER pour le danazol
Site de séquestration splénique ou hépato-splénique aux épreuves isotopiques si elles sont réalisées	OUI			

Légende explicative pour l'utilisation du tableau	
NON	Elément contre-indiquant le choix de ce traitement de deuxième ligne
A EVITER	Elément amenant à déconseiller le choix de ce traitement
	Element sans influence déterminante sur le choix de ce traitement
OUI	Element amenant à fortement conseiller le choix de ce traitement

Objectifs pour le futur

- **Meilleure connaissance de la physiopathologie**

- **Identifier des facteurs pronostiques**
  - -Evolution vers la chronicité au moment du diagnostic
  - - Réponses aux traitements