

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

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CeReCAI:

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Service de Médecine Interne

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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

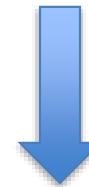
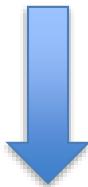
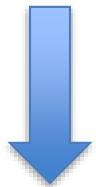
ITP duration

« Acute » 0 to 6 mths

Dg

3 mths

12 mths



Newly diagnosed
ITP

Persistant ITP

Chronic ITP

Mai 2017

**Protocole national de
diagnostic et de soins
(PNDS)**

**Purpura thrombopénique
immunologique de
l'enfant et de l'adulte**

Ce PNDS a été coordonné par le Pr Bertrand GODEAU du Centre de Référence des Cytopénies Auto-Immunes de l'adulte (CeReCAI) du CHU Henri Mondor de Créteil en collaboration avec le Dr Nathalie ALADJIDI, Centre de Référence des cytopénies auto-immunes de l'enfant (CEREVANCE, Pr Yves Pérel) et sous l'égide de la filière de santé maladies rares MARIH (Maladies Rares Immuno-Hématologiques).

Ce document est soutenu par la Société Française d'Hématologie (SFH), la Société Nationale Française de Médecine Interne (SNFMI) et par la Société d'Hématologie et d'Immunologie Pédiatrique (SHIP).

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

Les traitements de première ligne

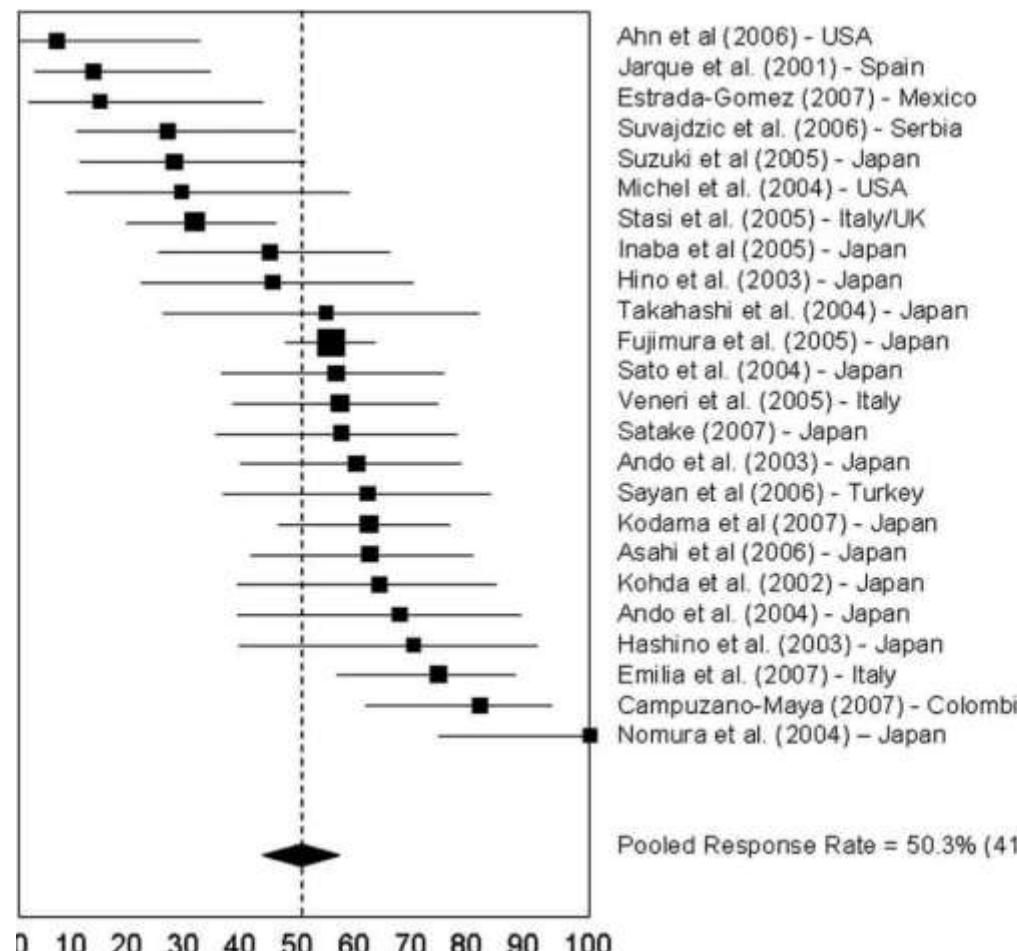
- **Prednisone**, 1mg/kg/j pendant 3 semaines puis arrêt rapide
- Ou **Dexamethasone**, 40mg/j pendant 4j
- **IgIV**: 1 à 2 g/kg réservées aux formes avec syndrome hémorragique grave
- **Transfusions de plaquettes** réservées aux formes avec mise en jeu du pronostic vital et en association avec les traitements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

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. Busse⁸



H. pylori and ITP

ORR: 50%

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

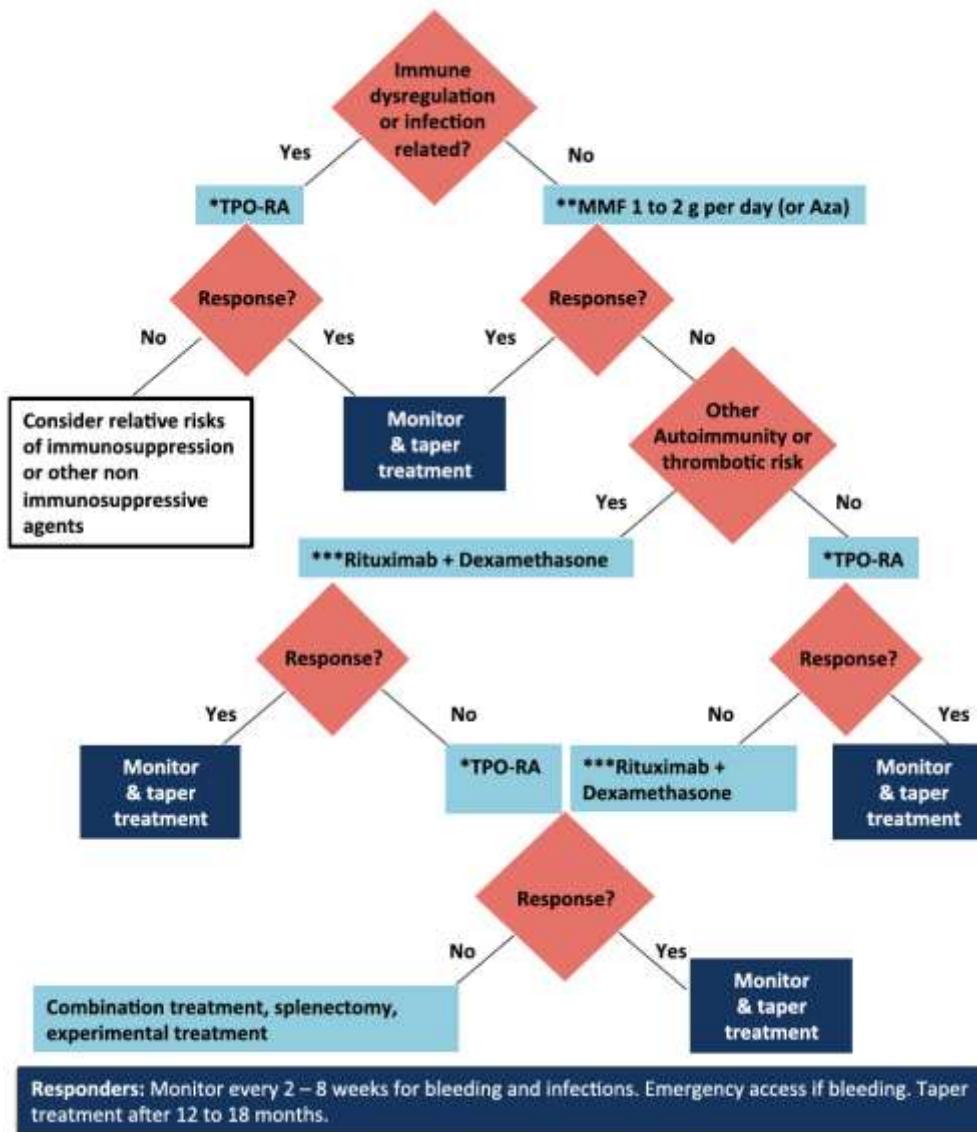
	Complete response	Response	No response
Primary ITP			
Total number of patients (29)	11	4	14
Number of previous lines of therapy (mean)	2.3	2	3.4
Time from diagnosis to MMF (mean, months)	60.8	163	31.3
Secondary ITP			
Total number of patients (17)	4	5	8
Number of previous lines of therapy (average)	4.3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

Overall
response rate:
52%

State of the art – how I manage immune thrombocytopenia

Nichola Cooper

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

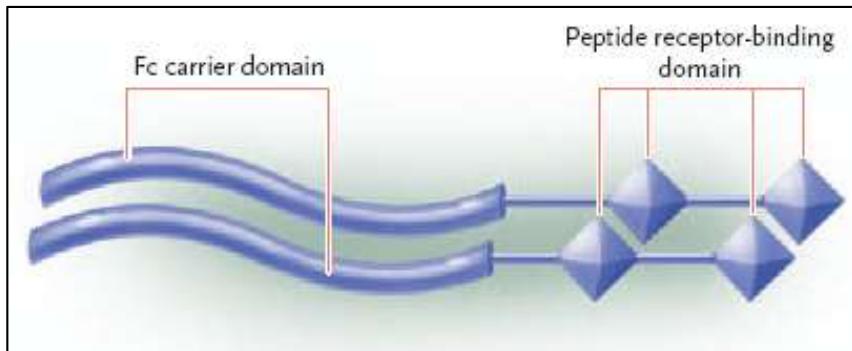


Responders: Monitor every 2–8 weeks for bleeding and infections. Emergency access if bleeding. Taper treatment after 12 to 18 months.

TPO-r agonistes

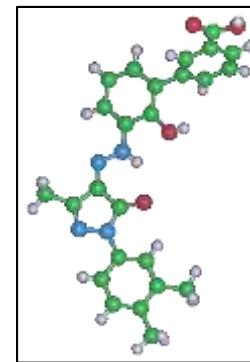
Romiplostim (Amgen®)

AMG 531



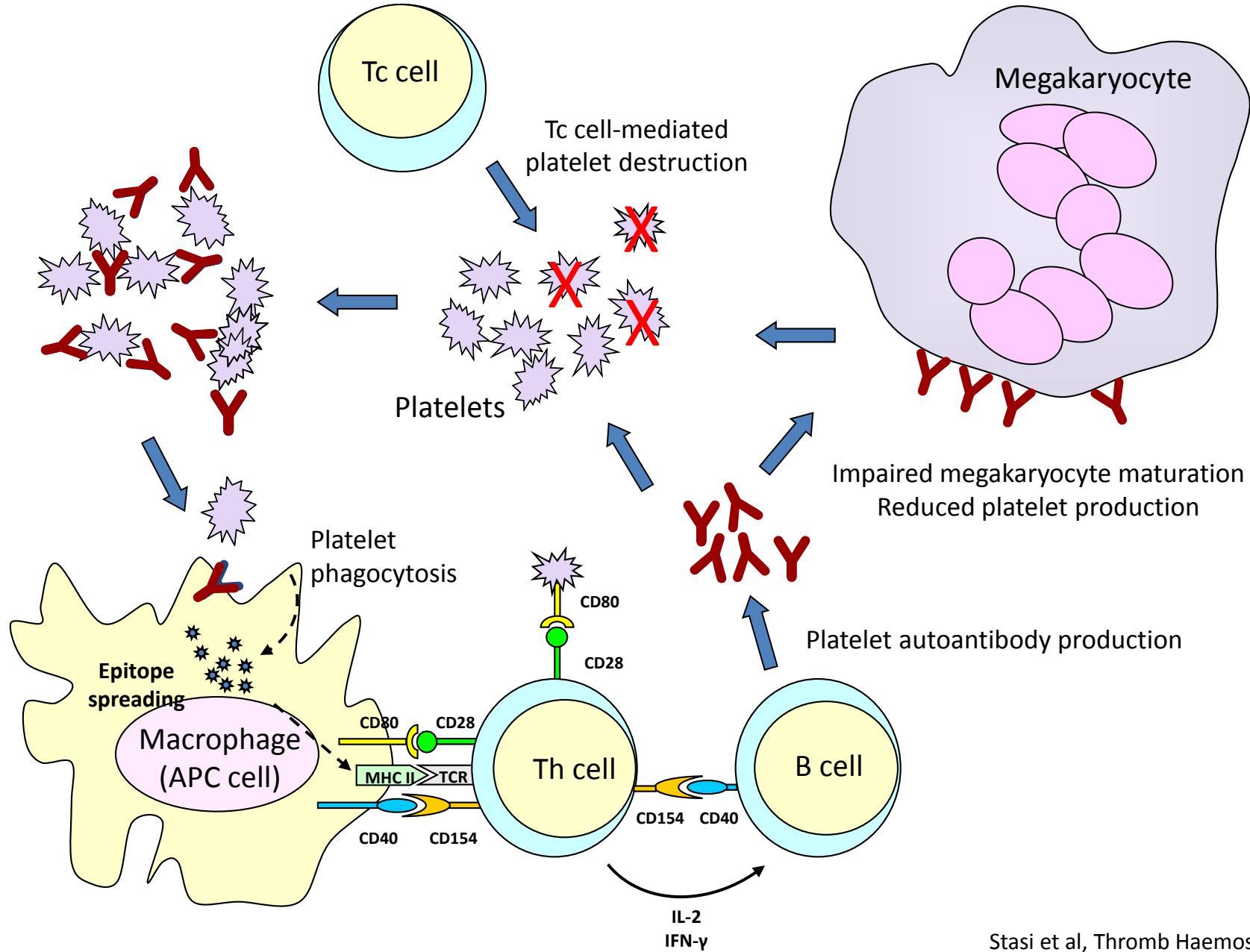
Partie Fc ↑ la demi-vie de la molécule
Voie sous-cutanée 1 fois par semaine
Dosage 1 µg/kg à 10 µg/kg

Eltrombopag (Novartis®)

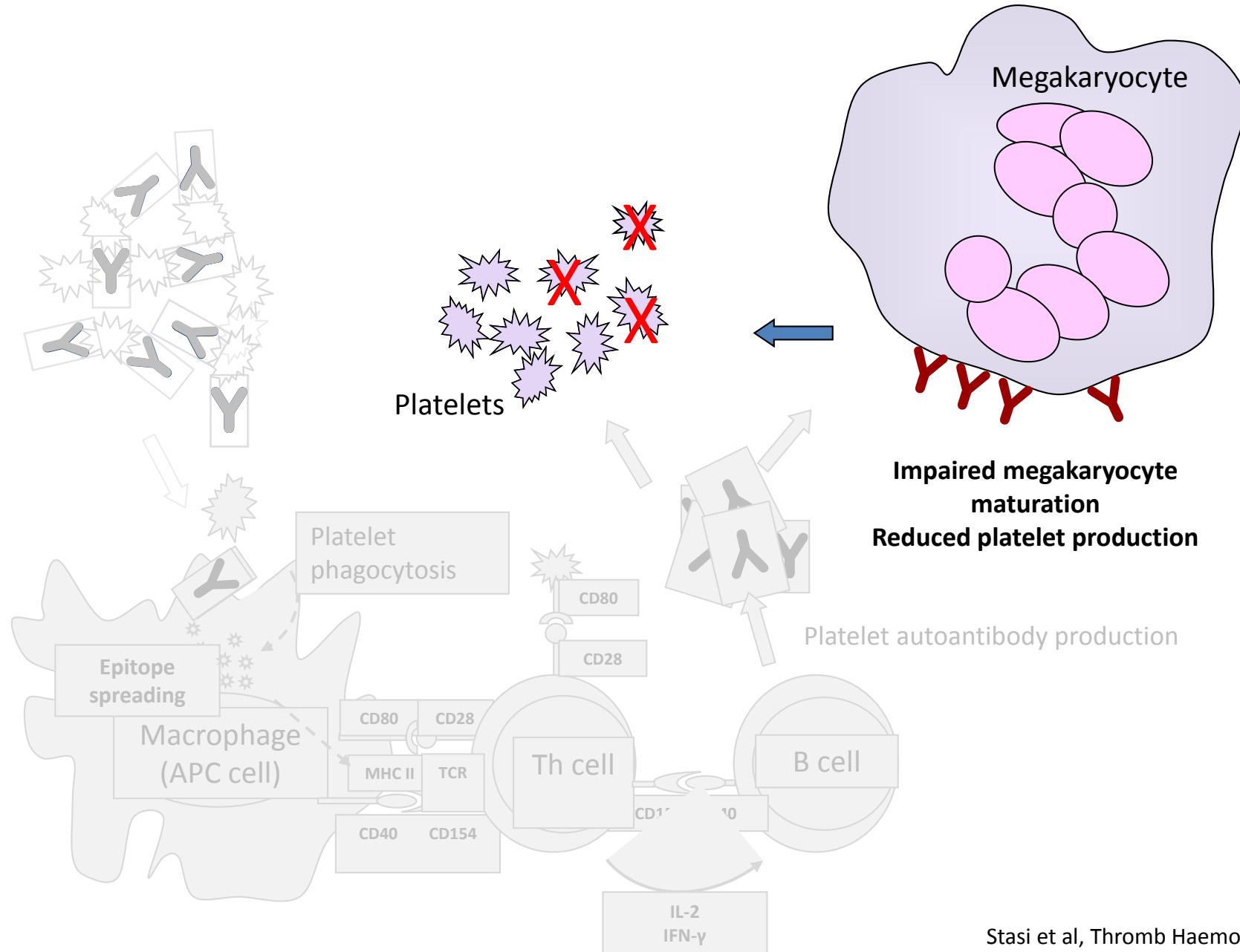


Voie orale quotidienne
Dosage 50 ou 75 mg

ITP Pathogenesis



ITP Pathogenesis



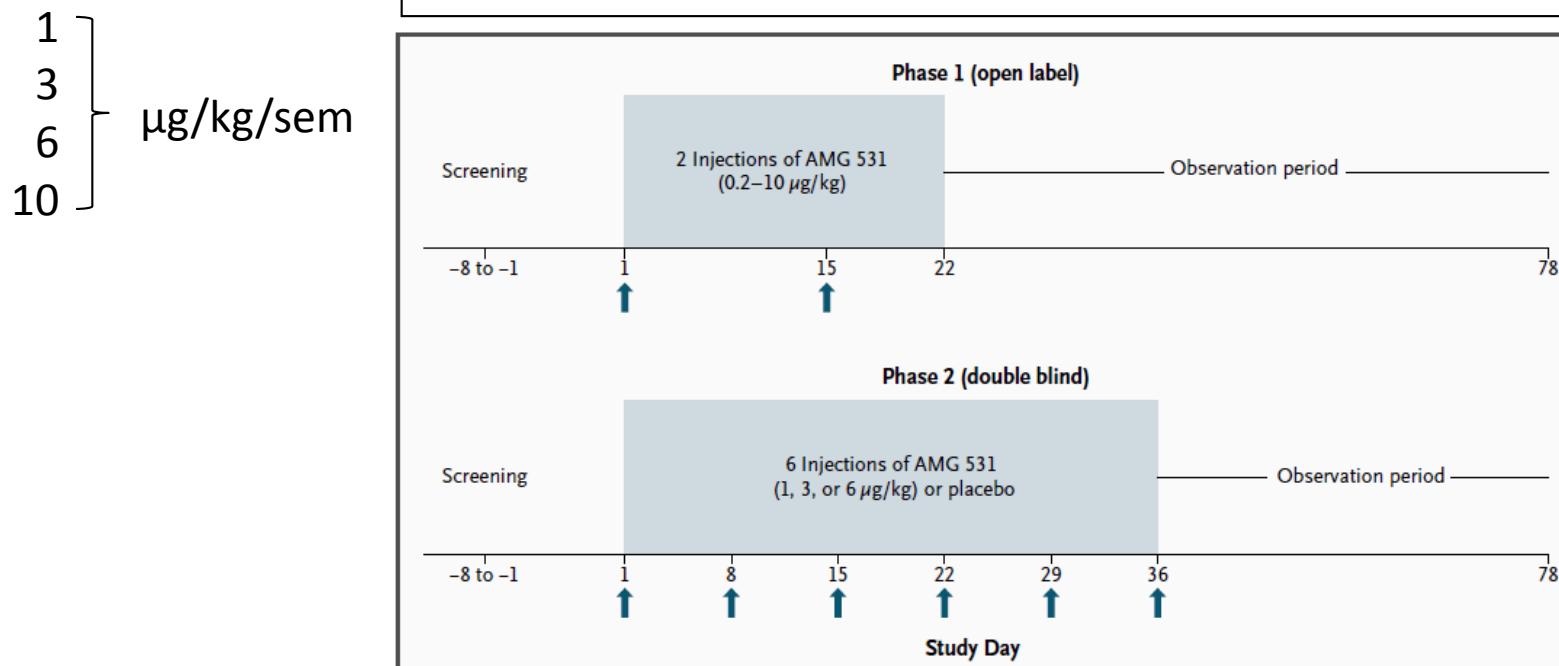
Romiplostim 1ers essais

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

The NEW ENGLAND JOURNAL of MEDICINE
2006; 355: 1672-81

ORIGINAL ARTICLE

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



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 $30 \times 10^9/L$ 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.

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

David J. Kuter, James B. Busiel, Roger M. Lyons, Vlado P. Mankoff, Terry R. Gersbachman, Francis A. Sereika, Louis M. Alford, Jones N. George, Craig M. Kessler, Miguel A. Sanz, Howard A. Leiberman, Frank T. Slevcik, J.D. M. de Weij, Environnement Bourgeois, Troy H. Gutierrez, Adrian Newland, Jeffrey P. Werner, Solomon L. Hunning, Charles Grapow, Josephine Lefebvre, Alan E. Lichten, Michael U. Tsoorino, Howard J. Treloar, Jean-François Valente, Franco Cavarini, Ronald S. Gao, Daniel H. Henry, Robert L. Redner, Lawrence Ro, Martin B. Schepers, D. Matthew Guo, Janet L. Nichols

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 $50 \times 10^9/L$ or less were randomly assigned 2:1 to subcutaneous injections of romiplostim ($n=42$) or placebo ($n=21$) in a splenectomy study and $n=41$ in a non-splenectomy study) or placebo ($n=21$ in both studies) every week for up to 24 weeks. Doses of study drug were adjusted to maintain platelet counts of $50 \times 10^9/L$ to $200 \times 10^9/L$. The primary objectives were to assess the efficacy of romiplostim as measured by a durable platelet response (platelet count $\geq 50 \times 10^9/L$ during 6 or more of the last 8 weeks of treatment) and treatment safety. Analysis was per protocol. These analyses are registered with ClinicalTrials.gov, numbers NCT00102332 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 23–45.2; $P=0.001$]), and by 23 of 41 non-splenectomised patients given romiplostim versus one of 21 given placebo (56% [38–77.3; $P<0.0001$]). The overall platelet response rate (either durable or transient platelet response) was noted in 83% (36/44) 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 $\geq 50 \times 10^9/\text{L}$ or more on a mean of 13.8 [SE 0.9] weeks (mean 13.3 [3.2] weeks in splenectomised group vs 15.2 [2.2] 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 characterized predominantly by antibody-mediated platelet destruction.¹⁻³ Available therapies—such as corticosteroids, intravenous immunoglobulin, splenectomy, rituximab, and cyclophosphamide—primarily focus on reduction of this platelet destruction.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,^{5,7} and thrombopoietin concentrations are normal or near normal in patients

with this disease.²² Moreover, antiplatelet antibodies inhibit *in-vitro* growth of megakaryocyte precursors cells,²³ and bone marrow megakaryocytes in ITP can be apoptotic.²⁴ 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 outcome in patients with this chronic disease.

Romiplostim (formerly known as AMG333) is a novel thrombopoiesis stimulating protein (peptibody) that binds to and activates the human thrombopoietin receptor despite having no sequence homology with human thrombopoietin.²⁰ Romiplostim reduces a

Lancet 2001; **357:** 399-401

See Comment page 302

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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 ($p<0.0001$).

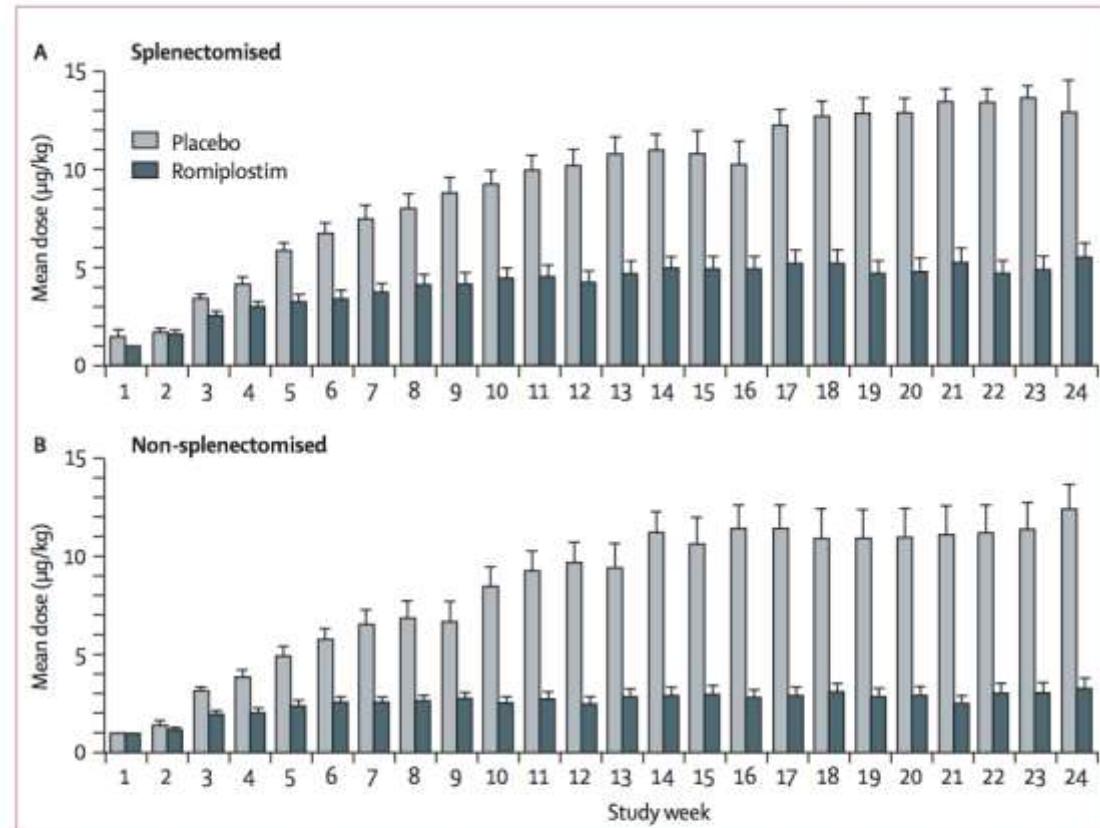


Figure 2: Mean dose of romiplostim or placebo per week at every study visit for splenectomised (A) and non-splenectomised (B) patients

Error bars show SEM. Throughout the 24-week study period, the median dose of romiplostim needed to maintain target platelet counts of $50\times10^9/L$ to $200\times10^9/L$ was roughly $3\text{ }\mu\text{g/kg}$ in splenectomised patients and $2\text{ }\mu\text{g/kg}$ 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

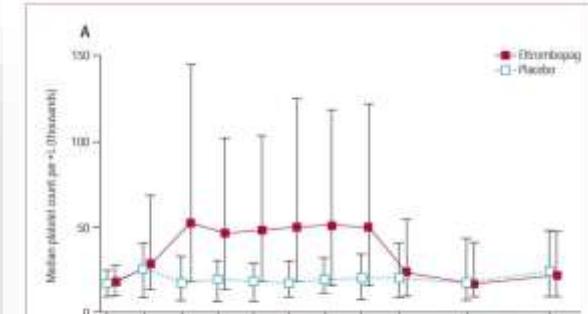


Figure 1A: Median platelet counts (A) and mean changes in platelet counts (B) at every visit*. Median platelet counts at every visit are shown with 95% CIs. Flu-follow-up. *Four patients who received eltrombopag and two who received placebo were still receiving study medication on or within 3 days before the day-50 assessment and were included in this analysis.

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. Nichol⁵

BLOOD 2009; 113: 2161-71

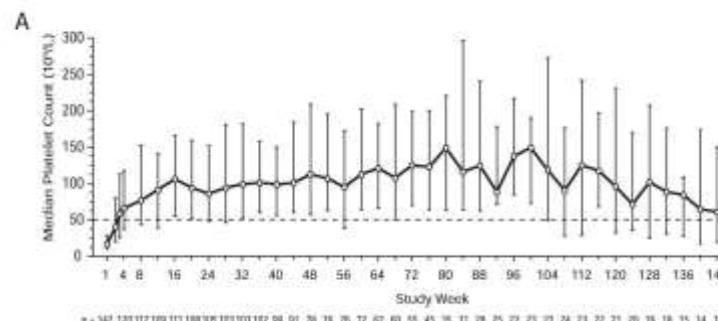


Figure 2. Platelet counts and platelet responses by study week. (A) Median (25th [Q1] and 75th [Q3] percentiles) platelet counts by study week. Median platelet counts increased sharply during the first 4 weeks of treatment and then more gradually through week 16. (B) Percentage of patients with a platelet response over time. A platelet response was defined as a platelet count of 50 + 10%, or more than 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 83% 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.

Khella 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 Khella¹, Marc Michel¹, Philippe Quittet², Jean-François Viallard³, Magda Alexis⁴, Françoise Roudot-Thoraval⁵, Stéphane Cheze⁶, Jean-Marc Durand⁷, François Lefrère⁸, Lionel Galicier⁹, Olivier Lambotte¹⁰, Gérard Panelatti¹¹, Borhan Slama¹², Gandhi Dama¹³, Gérard Sébahoun¹⁴, Emmanuel Gyan¹⁵, Xavier Delobel¹⁶, Nathalie Dhedin¹⁷, Bruno Royer¹⁸, Nicolas Schleinitz¹⁹, Jean-François Rossi²⁰, Matthieu Mehévas¹, Laetitia Languielle¹, Philippe Bierling²⁰ and Bertrand Godeau¹

¹Department of Internal Medicine, Centre Hospitalier Universitaire (CHU) Henri-Mondor, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris Est Crétell, Crétell, France; ²Department of Hematology, CHU Liége, Montpellier, France; ³Department of Infectious Diseases, CHU Haut-Lévêque, Pessac, France; ⁴Department of Hematology, CHU de Source, Orléans, France; ⁵Department of Public Health, Université Paris Est Crétell, Crétell, France; ⁶Groupe Francophone des Myélodysplasies, Caen, France; ⁷Department of Internal Medicine, Hôpital de la Conception, Assistance Publique-Hôpitaux de Marseille (AP-HP), Marseille, France; ⁸Department of Hematology, CHU Necker, AP-HP, Paris, France; ⁹Department of Hematology, CHU Saint-Louis, AP-HP, Paris, France; ¹⁰Department of Internal Medicine, CHU de Pitié-Salpêtrière, AP-HP, Paris, France; ¹¹Department of Hematology, CHU Fort de France, Fort de France, France; ¹²Department of Hematology, Centre Hospitalier (CH) d'Avignon, Avignon, France; ¹³Department of Hematology, CHU d'Amiens, Amiens, France; ¹⁴Department of Hematology, CHU Hôpital Nord, AP-HP, Marseille, France; ¹⁵Department of Hematology, CHU de Tours, Tours, France; ¹⁶Department of Rheumatology, CH de Pau, Pau, France; ¹⁷Department of Hematology, CHU Hôpital Pitié-Salpêtrière, AP-HP, Paris, France; ¹⁸Department of Hematology, CHU Henri-Mondor, AP-HP, Crétell, 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 $\geq 50 \times 10^9/L$ 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 $106 \times 10^9/L$ (interquartile range, $75-167 \times 10^9/L$), and 10 (21%) were still taking romiplostim, despite a median platelet count of $38 \times 10^9/L$ (interquartile range, $35-44 \times 10^9/L$), 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 peptide 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 studies⁹⁻¹² 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.

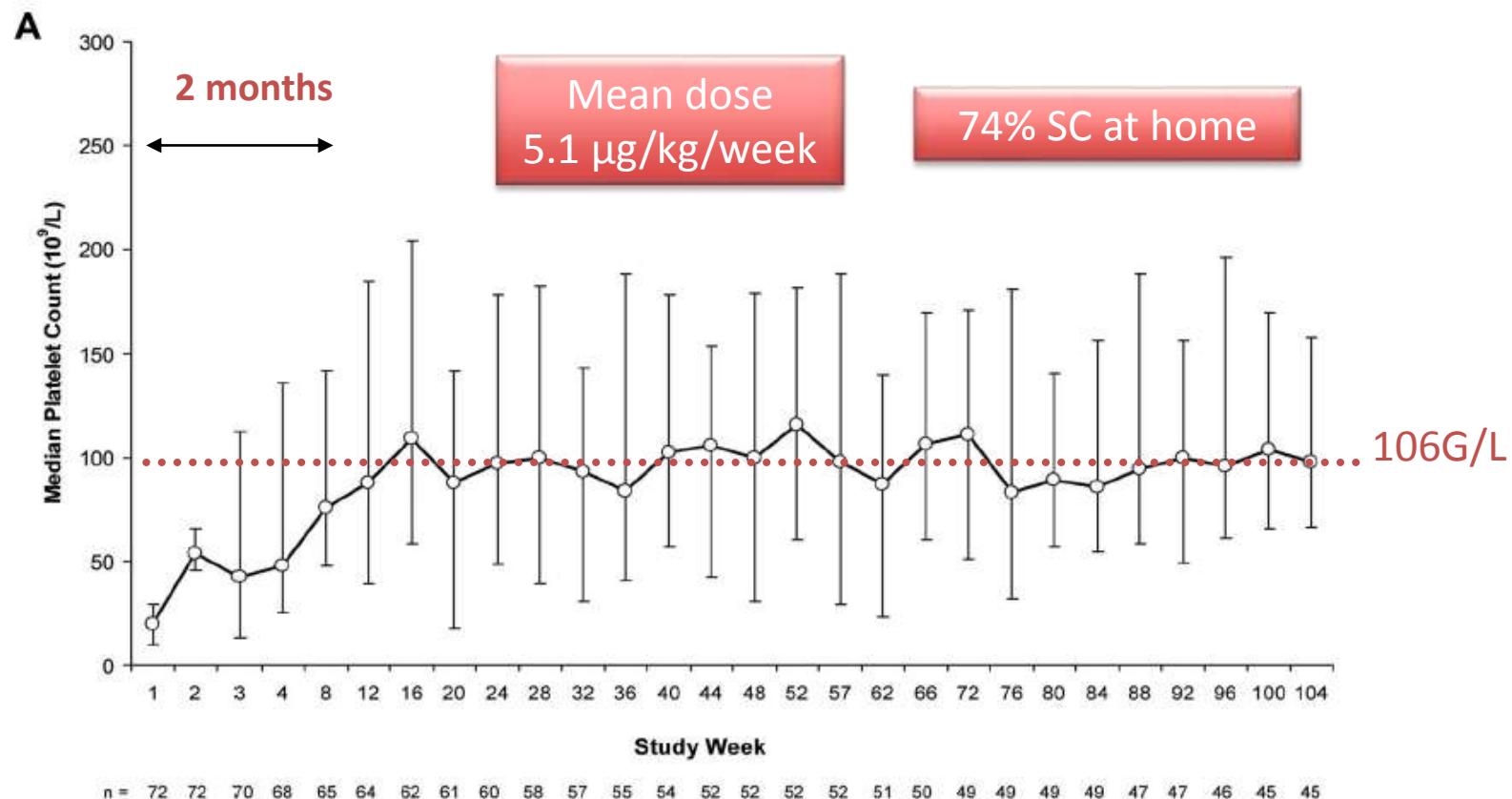
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Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a romiplostim compassionate-use program.

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



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

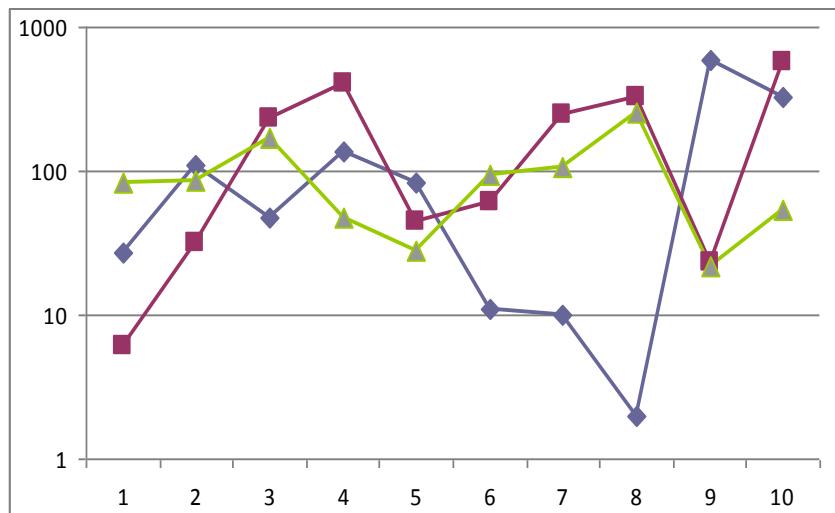
Questions non résolues

- Causes des échecs
- Réponse à long terme possible ?

Platelet fluctuation and TPO-r mimetics

Why ?

Log Plaq G/L

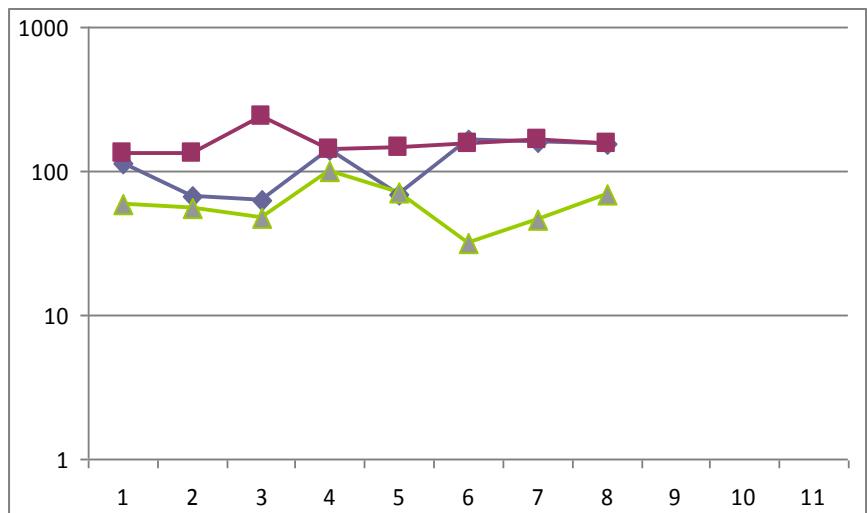


TPO-r mimetic n°1



TPO-r mimetics n°2

Log Plaq G/L



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 *et al*, Int J Hematol 2015

ARTICLES

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

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ABSTRACT

Switching and discontinuing the first thrombopoietic receptor-agonists with demonstrated efficacy against immune thrombocytopenia in prospective controlled studies, were recently authorized in many countries for adults with chronic immune thrombocytopenia. So far, no data are available about the potential contribution of switch or discontinuation to discontinuing or re-treatment in terms of efficacy or tolerance. Efficiency and tolerance profiles were analyzed in 25 patients who discontinued or discontinued after 31 days of treatment with eltrombopag or romiplostim, or switching from eltrombopag to romiplostim, or vice versa for 31, 6, and 8 patients, respectively. For 95.2% of the patients, switching from romiplostim to eltrombopag or vice versa was well-tolerated and effective. For 10.4% of the patients, the thrombopoietic receptor-agonist was discontinued because of adverse events. Our results confirmed that switching from one thrombopoietic receptor-agonist to the other could be performed in clinical practice for patients with severe chronic immune thrombocytopenia who failed to respond or experienced adverse events to the first. © 2013 The Authors. *Journal of Internal Medicine* © 2013 Royal Society of Medicine. *J Intern Med* 273: 67–75.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by low platelet counts and varying degrees of mucocutaneous bleeding. ITP treatment has long been considered to be only a series of accidental placebo discoveries by practitioners, probably due to the lack of knowledge of the pathophysiology of "immune thrombocytopenia".¹ Most therapies currently used to treat ITP, e.g., corticosteroids, intravenous immunoglobulin (IVIG), immunosuppressive and plateletpheresis, have been developed based on the experience with body-coated platelets. In contrast, the novel thrombopoietic receptor-agonists (TPO-RA) are synthetic plerelin derivatives.²

In order to derive very good results, in an observational study on romiplostim, we showed that therapy on site and individual approach may be more effective than the off-site home treatment.³ Because romiplostim and eltrombopag act differently on the TPO-RA and the 2 molecules have not been directly compared, the relevance of switching between TPO-RA or the other in clinical practice has not been

widely acknowledged.⁴ Eltrombopag is a non-erythropoietin TPO-RA that is a 447 Da drug that binds to a transmembrane site on the TPO-2, thereby activating it. It is interesting to note that the first TPO-RA to be approved had the expected response rates to romiplostim and eltrombopag being over 80% and their efficacy was achieved in subjects treated and non-treatment-naïve ITP patients.⁵ In view of the high efficacy of romiplostim and eltrombopag in adult chronic ITP in more than 80% patients and their great safety, these overall figures for chronic ITP.⁶ However, as far as we are only interested in the use after splenectomy, the number of patients is much smaller.

In contrast to derive very good results, in an observational study on romiplostim, we showed that therapy on site

and individual approach may be more effective than the off-site home treatment.³ Because romiplostim and eltrombopag act differently on the TPO-RA and the 2 molecules have not been directly compared, the relevance of switching between TPO-RA or the other in clinical practice has not been

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Use of eltrombopag after romiplostim in primary immune thrombocytopenia

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Summary

The thrombopoietic receptor agonist (TPO-RA), romiplostim and eltrombopag, are effective and safe in chronic thrombocytopenia (ITP). However, the value of their sequential use when no response is achieved or when adverse events occur with one TPO-RA has not been clearly established. Here we retrospectively evaluated 35 patients (ITP) with patients treated sequentially by eltrombopag. The median age of our patients was 40 (range 4–61) and the median platelet count was 23 (interquartile range 9–32) × 10⁹/L. The reasons for switching were: lack of efficacy ($n = 20$), patient preference ($n = 10$), physician preference ($n = 9$) and side effects ($n = 4$). The response rate to eltrombopag was 95.5% (34/36). Including 36% ($n = 13$) complete responses. After a median follow-up of 44 months, 31 patients maintained their response. Physician preference was the main reason for the switch. However, cumulative administration of patients in the eltrombopag group was higher. There were no significant late 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 thrombopenia discrimination.

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

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ORIGINAL ARTICLE

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

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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 the other. We also assessed the risk of thrombocytopenia in patients with chronic ITP who discontinued romiplostim or eltrombopag. The study examined the rationale for switching to TPO-RA therapy using solid responses. Thrombopenia rates were also analyzed before and after switching. Treatment outcomes were assessed through physician counts at multiple time points including treatment initiation and after switching at the last office visit. A total of 280 patients were enrolled when active therapy for ITP was replaced with either eltrombopag ($n = 130$) or romiplostim ($n = 150$). Eltrombopag-treated patients (switched patients) achieved a higher rate of response to eltrombopag than romiplostim patients (75.0% vs. 57.7% for romiplostim). Patients counts at the last office visit showed improvement in response with switch at the initiation of either eltrombopag or romiplostim treatment. No significant difference was found 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.

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

Introduction

Immune thrombocytopenia (ITP) is maintained in about 60,000 adult patients in the United States [1]. It is characterized by low platelet counts and the associated risk of bleeding. For patients with chronic ITP, the predominantly low platelet counts present real and perceived risks for venous and/or oral/soft tissue bleeding events [2], and may therefore require emergency department visits and hospitalizations [3]. Decreased platelet counts, chronic symptoms, and treatment side effects have a notable impact on the overall quality of life for patients with ITP [2, 3, 4].

For these patients, the standard of care is the discontinuation of ITP treatment [5].

For those who do not respond to the discontinuation of ITP, including romiplostim or eltrombopag [6, 7], corticosteroids are usually only given for a few months



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

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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.

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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 (Buddebohm *et al*, 2009, 2013; Khalaf *et al*, 2013; Salib *et al*, 2013). Eltrombopag is an oral, synthetic non-peptide agonist that binds the trans-membrane domain of the Tpo receptor (Bassel *et al*, 2007). Romiplostim is a peptide 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 to be effective in chronic liver disease-associated thrombocytopenia (McHughan *et al*, 2007; Sample *et al*, 2012). Moreover, encouraging published data have shown that eltrombopag may improve haemopoiesis in refractory aplastic anaemia (Oliver *et al*, 2012). The mechanism of action of Tpo-RAs means that the platelet count

TPO-mimétiques et thrombose

Situations à risque?

- Lupus, SAPL → Risque de thrombose si APL+++
- 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 mimétiques 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 pathophysiological mechanisms involved. This complex topic encompasses diverse underlying conditions for which splenectomy is performed, diverse thrombotic complications, and multiple pathophysiological 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.

steroids 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 2005.¹ In most institutions, trauma and incidental splenectomy are the primary indications,² 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.

Asplenia and hypsplenism

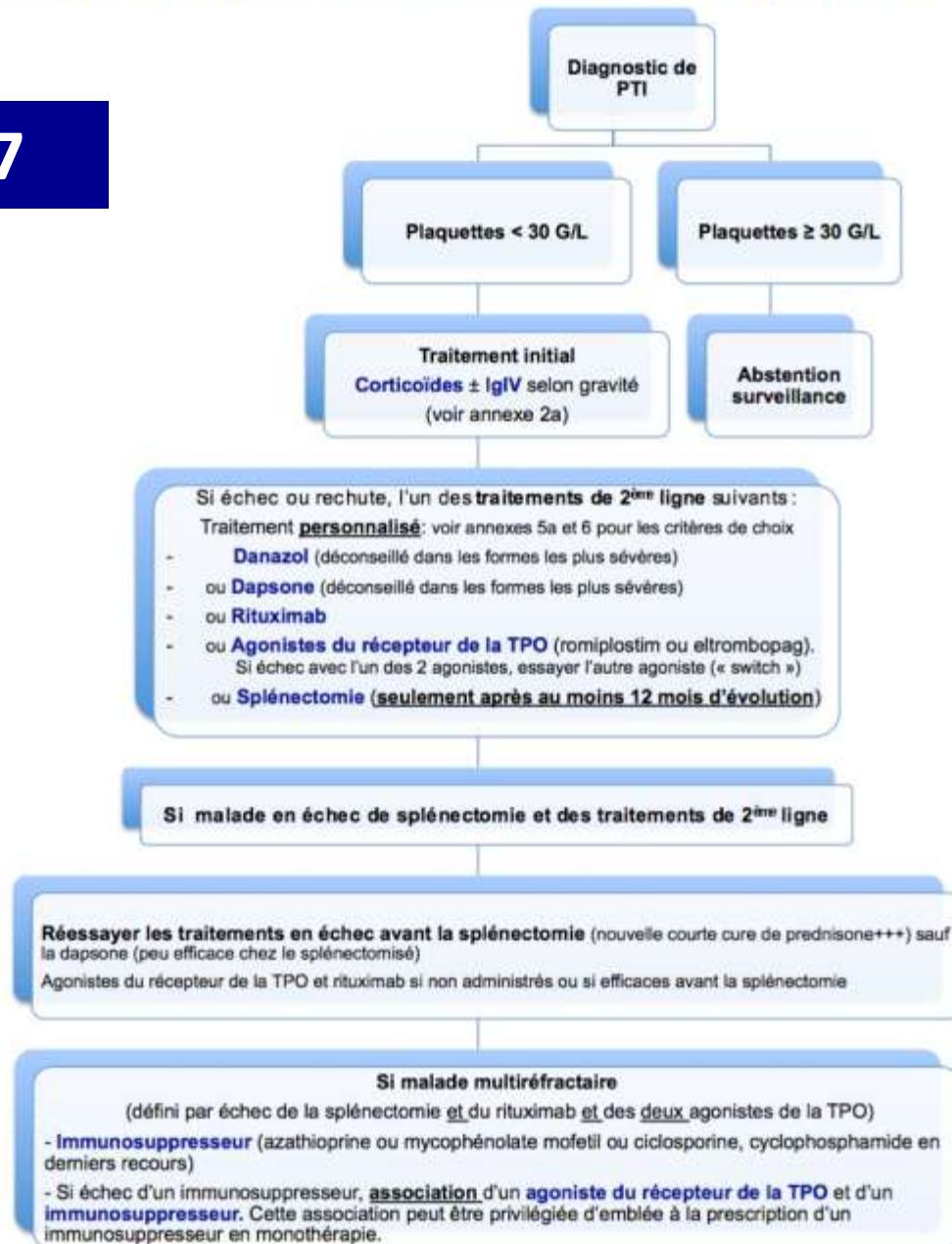
Congenital asplenia can occur in isolation or may be associated with certain forms of congenital heart defects or heterotaxy syndromes.⁴ Children with sickle cell disease have acquired hypsplenism that begins at several months of age and progresses to splenic infarction. Young patients with sickle cell 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 hypsplenism may also occur during therapy with cortico-

Septic risk of asplenia and hypsplenism

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 hypsplenism 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



Annexe 6.

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

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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 hépatosplénique 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
À EVITER	Elément amenant à déconseiller le choix de ce traitement
	Elément sans influence déterminante sur le choix de ce traitement
OUI	Elément 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