PURPURA THROMBOCYTOPENIQUE IMMUNOLOGIQUE

Congrès Maghrébin d'hématologie
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PURPURA THROMBOCYTOPENIE IMMUNOLOGIQUE

NOTIONS FONDAMENTALES

1. Thrombopénie **auto-immune** acquise
2. **Primitive** ou secondaire
3. Touche toutes les tranches d'âge
4. Clinique variable selon l'âge
5. Stratégie thérapeutique W & W → analogues thrombopoeitine

Points discutés

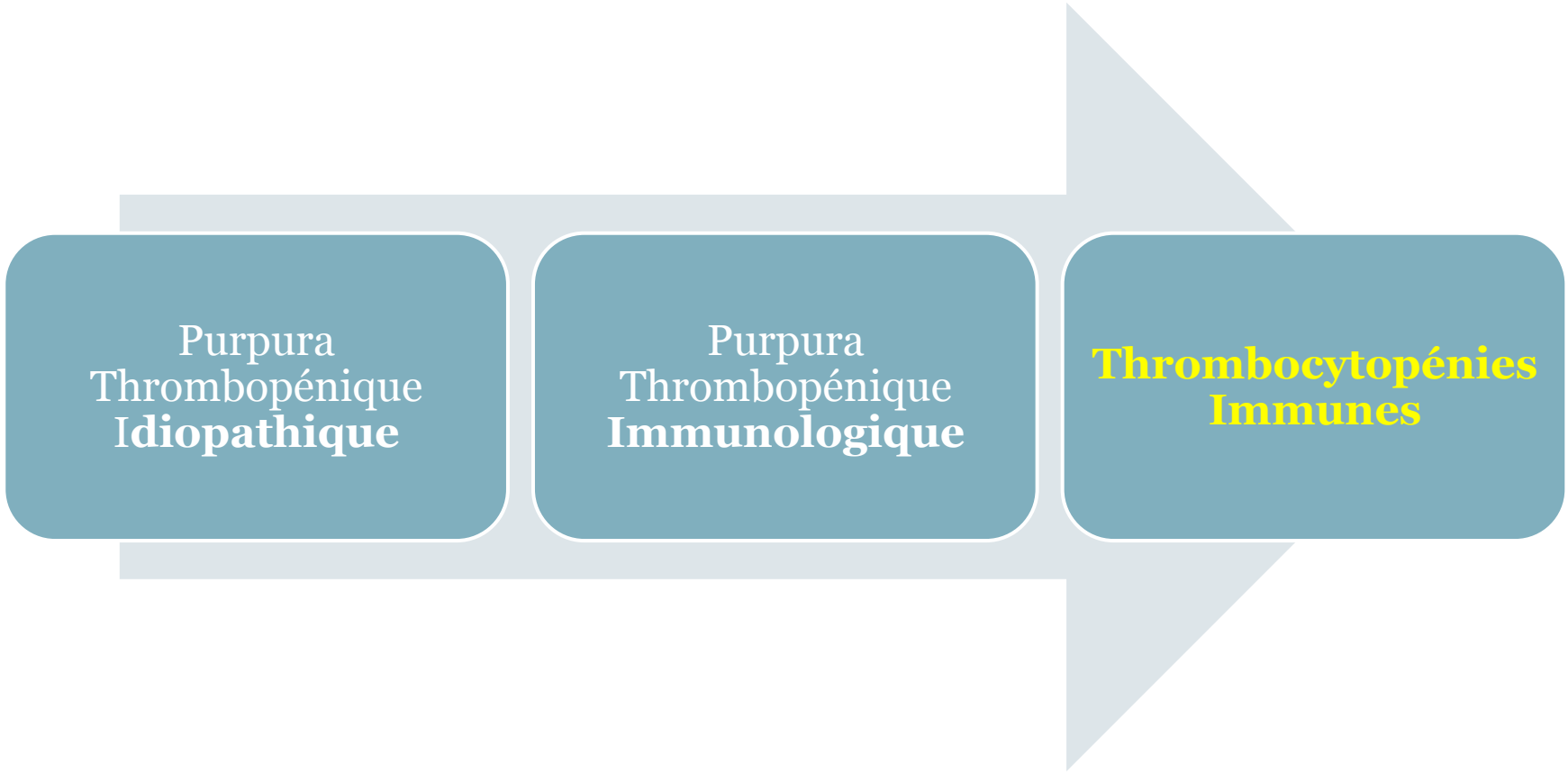
1. Définitions et terminologies
2. Epidémiologie
3. Présentation clinique et Explorations
4. Alternatives thérapeutiques
5. Conclusion

1 - TERMINOLOGIE

Thrombocytopénies

Immunologiques

Evolution de la terminologie



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

Diagnosis and management of immune thrombocytopenic purpura (ITP) remain largely dependent on clinical expertise and observations more than on evidence derived from clinical trials of high scientific quality. One major obstacle to the implementation of such studies and in producing reliable meta-analyses of existing data is a lack of consensus on standardized critical definitions, outcome criteria, and terminology. Moreover, the demand for comparative clinical trials has dramatically increased since the introduction of new classes of therapeutic agents, such as thrombopoietin receptor agonists, and innovative treatment modalities, such as anti-CD 20 antibodies. To overcome the present heterogeneity, an International Working Group of recognized expert clinicians convened a 2-day structured meeting (the Vicenza Consensus Conference) to define standard terminology and definitions for primary ITP and its different phases and criteria for the grading of severity, and clinically meaningful outcomes and response. These consensus criteria and definitions could be used by investigational clinical trials or cohort studies. Adoption of these recommendations would serve to improve communication among investigators, to enhance comparability among clinical trials, to facilitate meta-analyses and development of therapeutic guidelines, and to provide a standardized framework for regulatory agencies. (Blood. 2009;113:2386-2393)

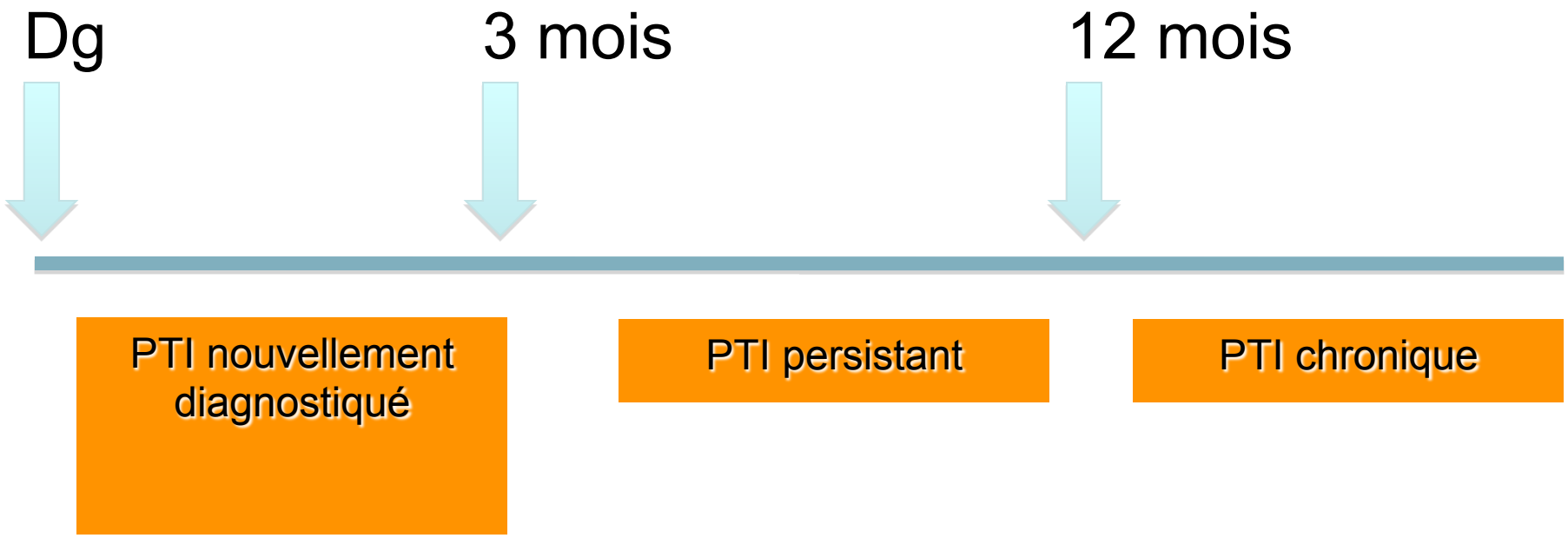
Blood 2009; 113: 2386-2393

Abécédaire des thrombopénies immunes

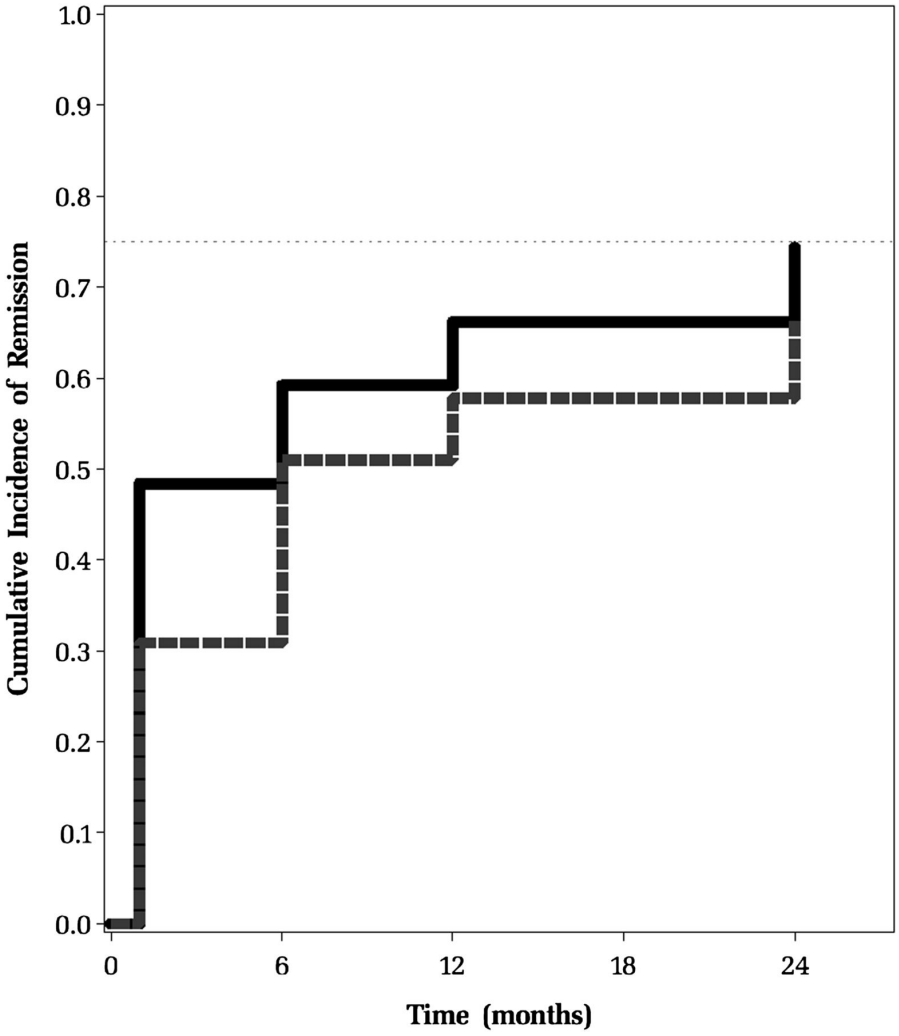
Terme	commentaire
Thrombocytopénie immune **I**mmune **T**hrombocyto**P**énia **ITP**	Remplace le terme ***purpura thrombopénique immunologique*** ou idiopathique
PTI récemment diagnostiqué	Remplace le terme ***PTI aigue***
PTI persistant	PTI avec plaquettes < 100 000/ mm3 Pendant ***3 à 12 mois***
PTI chronique	PTI avec plaquettes < 100 000/ mm3 Pendant ***plus de 12 mois***

Breakey. Semin in Thromb & hem 2011

Evolution de la terminologie



Cumulative incidence of remission.



Neunert C E et al. Blood 2013;121:4457-4462

2 - EPIDEMIOLOGIE

- Incidence 3 – 5 / 100 000 enfant/ an
- Incidence variable selon
  - Âge
  - Sexe
  - Saison
- 1er pic d'incidence entre 1 – 6 ans
- TI secondaires sont « rares » chez l'enfant

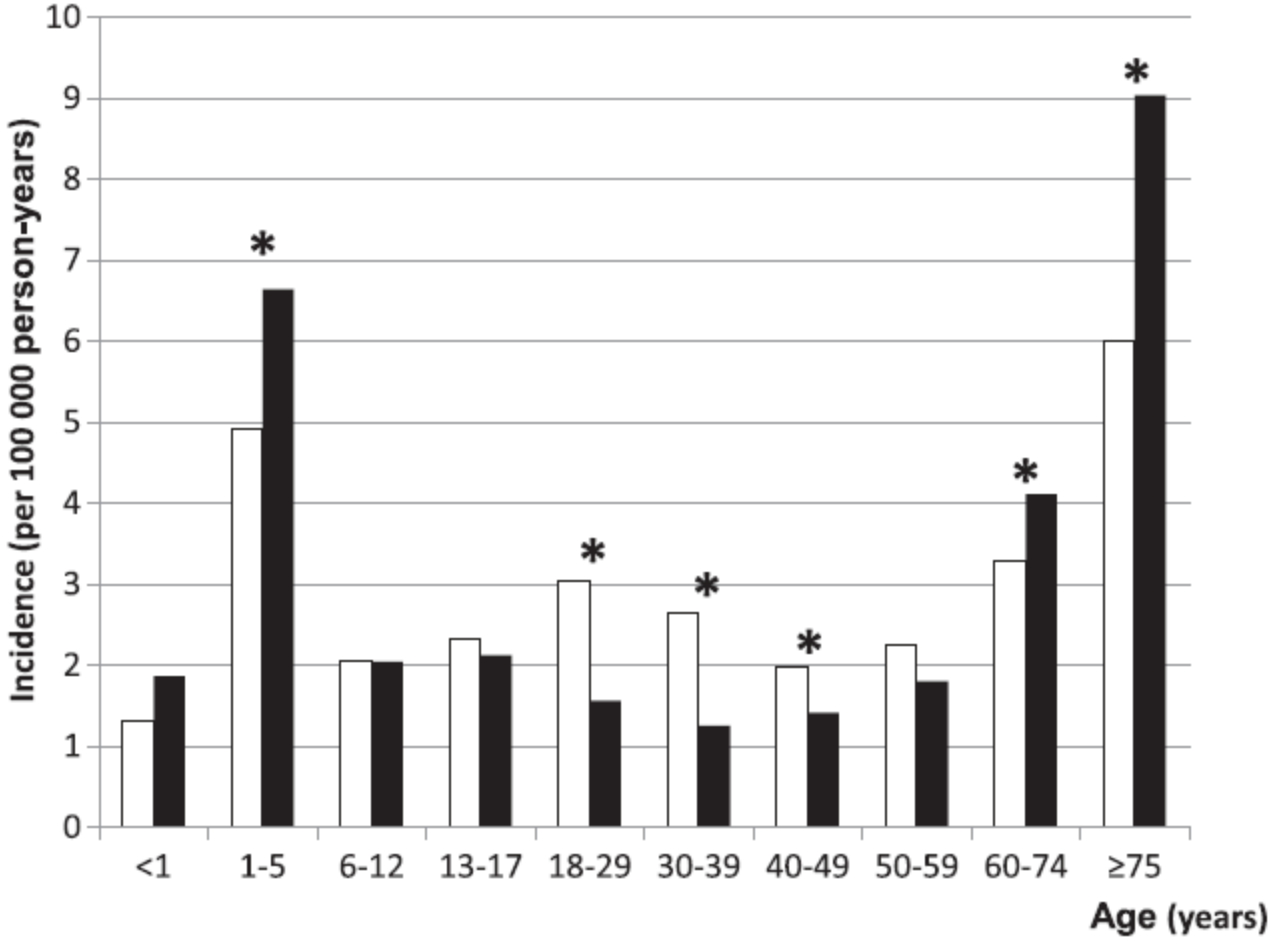
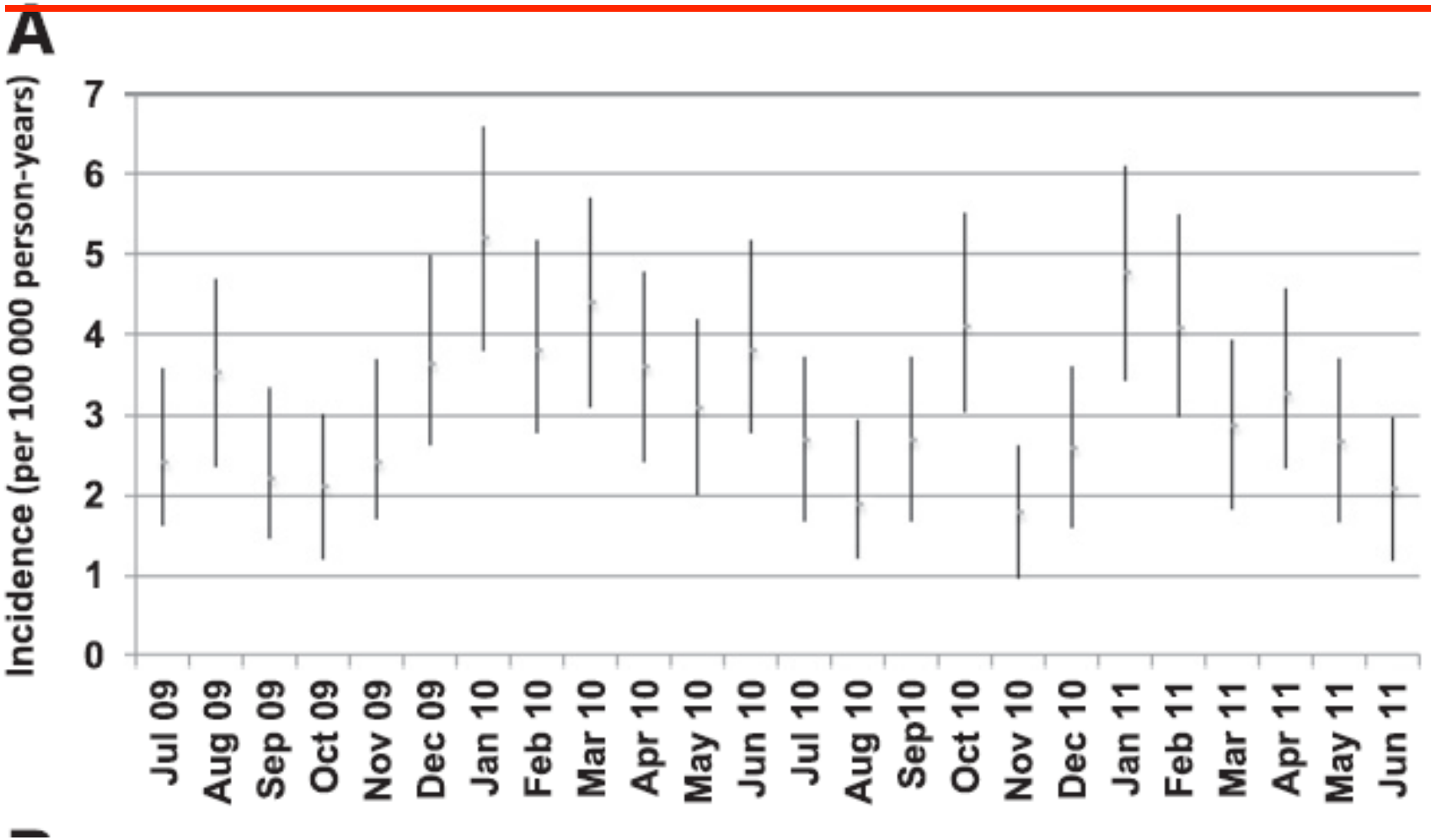


Figure 2. Incidence of ITP in France during the period from mid-2009 to mid-2011 by age and gender. Females, white bars; males, black bars. Stars indicate statistically significant differences among males and females (α = 5%).

Moulis G et al, Blood 2014

Seasonality of ITP in children



Moulis G et al, Blood 2014

3- CLINIQUE ET EXPLORATIONS

Symptom	Number of children presenting with symptoms	
Bruising	386 (90·4%)	**Ecchymoses**
Purpura or petechiae	310 (72·6%)	**Pétéchies**
Nose bleeds	85 (19·9%)	**Epistaxis**
Bleeding from mouth, gums, or tongue	68 (15·9%)	
Other	11 (2·6%)	
Gastrointestinal bleeding*	10 (2·3%)	
Other non-bleeding-related symptoms	8 (1·9%)	
Conjunctival haemorrhage	7 (1·6%)	
Haematuria	6 (1·4%)	
Heavy periods	3 (0·7%)	
Bleeding ear	2 (0·5%)	

*Haematemesis, melaena, rectal bleeding, or blood on nappy.

Table 1: **Symptoms at presentation in 427 children**

Bolton-Maggs The Lancet 1997

Sévérité en fonction de la **clinique**

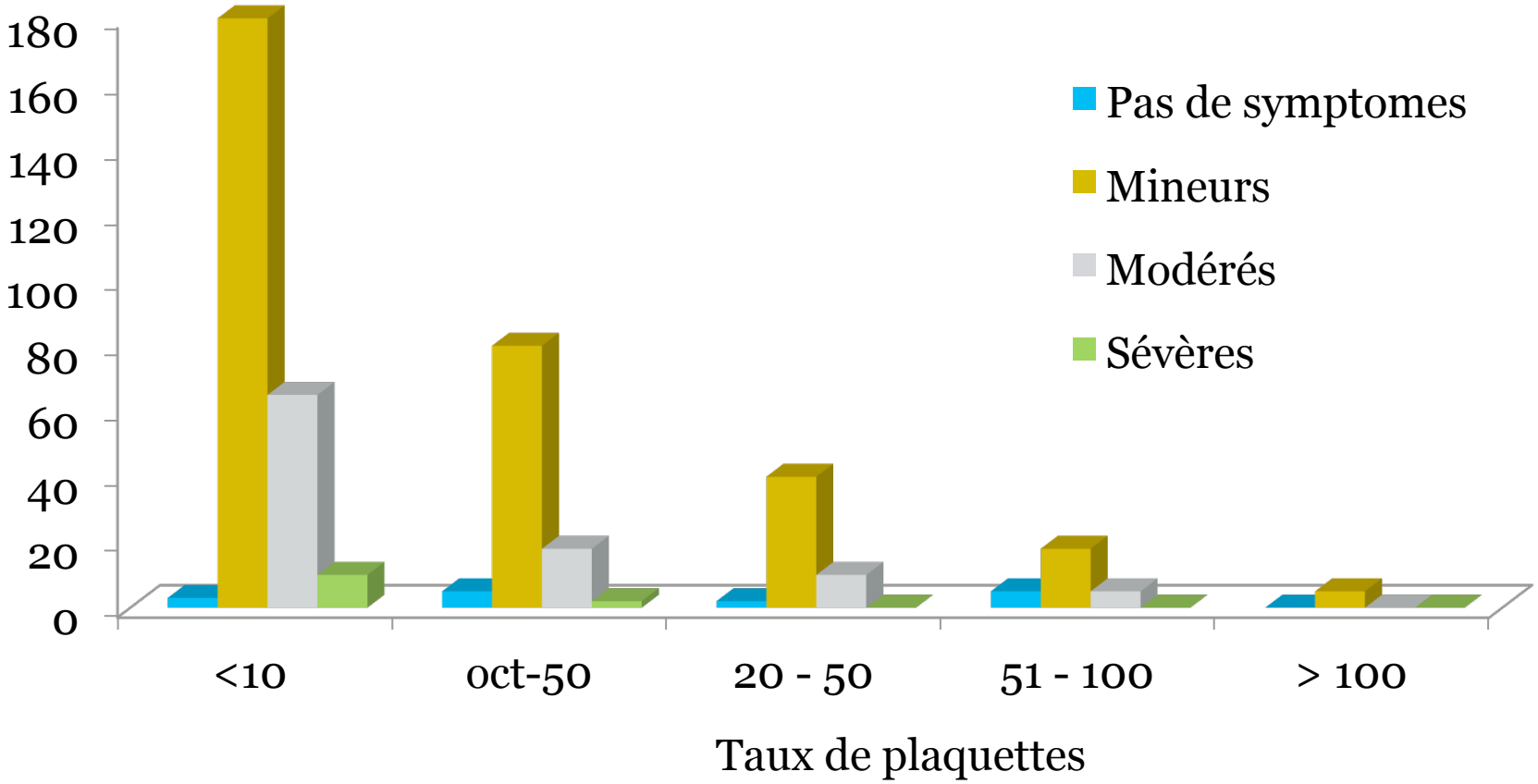
sévérité	Manifestations clinique
absente	Absence de signes hémorragiques
minime	Pétéchies et ecchymoses Epistaxis modéré occasionnel Peu de répercussions sur la qualité de vie
modérée	Lésions cutanées plus sévères Quelques lésions muqueuses
sévère	Syndrome hémorragique nécessitant une hospitalisation et/ ou transfusion Retentissement sur la **qualité de vie**

Buchanan, J Pediatr Hematol Oncol, 2003

Score de Buchanan

Grade	Sévérité du saignement	Description clinique
0	Aucun	Aucun signe
1	Mineur	Peau : ≤ 100 pétéchies ou ≤ 5 ecchymoses (≤ 3 cm de diamètre) Muqueuses : normales
2	Peu sévère	Peau : > 100 pétéchies ou > 5 ecchymoses (> 3 cm de diamètre) Muqueuses : normales
3	Modéré	Atteinte des muqueuses (épistaxis, bulles intrabuccales, hématurie, métrorragies…)
4	Sévère	Atteinte des muqueuses nécessitant un geste Suspicion d'hémorragie interne
5	Pronostic vital en jeu	Hémorragie intracrânienne ou hémorragie interne

Pas de corrélation entre la profondeur de la thrombopénie et la sévérité du tableau clinique



Hémorragie Intra-Craniennes?

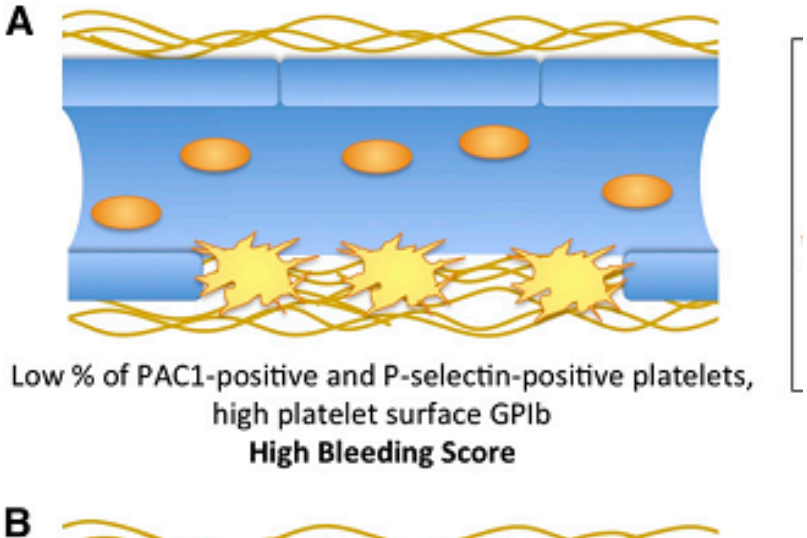
- Intercontinental ITP study group HIC = 0.17%
- Facteurs de risque
  - Trauma crânien
  - Prise d'aspirine ou AINS
  - Hématurie
  - Plaquettes < 10 000 éléments/mm3
- HIC survient indépendamment du traitement
- Mortalité inchangée avant/ après introduction des Immunoglobulines

- Etude récente, EU, en partie prospective < 17 ans, 1987 →2000
- Incidence 0,2 à 0,8 %
- Phase de survenue :
  - 18 (45 %), PTI aigu (10 ≤ 1ère semaine)
  - 12 (30 %), PTI > 6 mois
- Facteurs de risque :
  - Trauma crânien : 13 (30 %) surtout si < 3 ans
  - Hématurie : 9 (22 %)
- Evolution :
  - Mortalité : 10 (25 %)
  - Séquelles : 10 (25 %)

Diapo Guy Leverger

Platelet function tests, independent of platelet count, are associated with bleeding severity in ITP

Andrew L. Frelinger III,[1,2] Rachael F. Grace,[2] Anja J. Gerrits,[1,2] Michelle A. Berny-Lang,[1,2] Travis Brown,[2] Sabrina L. Carmichael,[1,2] Ellis J. Neufeld,[2] and Alan D. Michelson[1,2]



BLOOD, 13 AUGUST 2015 · VOLUME 126, NUMBER 7

Activated Platelet:
PAC1-positive,
P-selectin-positive
low surface GPIb

Prédictif d'un faible risque de saignement

Quelles explorations?

Numération formule sanguine

- **Thrombopénie isolée**
- Taux de GB + formule (PNN) normaux
- Hémoglobine et hématocrite
  - Anémie modérée si saignement important
  - Si anémie sévère → AHAI associée?
  - Taux de reticulocytes normal
- Plaquettes
  - Thrombopénie souvent profonde
  - VPM normal ou élevé
- Frottis sanguin → **aspect des plaquettes**

Médullogramme ?

Medullogramme indiqué si:

- **Présentation clinique atypique**
  - Anomalies squelettiques/dysmorphie
  - Fièvre, douleur osseuse
  - Anomalies des GB
  - VGM élevé
- **Avant la corticothérapie?**
  - Dubansky 1989 → sur 2000 cas de leucémie aucun cas de thrombopénie isolée
  - Watts 2004 → 296/402 médullogramme sans aucun impact sur le Dc/traitement
- **Non réponse au traitement**

Autres explorations à discuter

- **Ac antiplaquettes → aucun apport**
- Groupage ABO – Rh
- TCD
- LDH et acide urique
- Ionogramme, fonction hématique et rénale
- Recherche H Pilori chez l'enfant ?
- Serologie HIV
- Dosage pondéral des Ig
- Ac antinucléaires..

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

Whether the eradication of *Helicobacter pylori* infection can increase the platelet count in patients with immune thrombocytopenic purpura (ITP) is still a controversial issue. To provide evidence-based guidance, we performed a systematic review of the literature published in English, selecting articles reporting 15 or more total patients. We identified 25 studies including 1555 patients, of whom 696 were evaluable for the effects of *H pylori* eradication on platelet count. The weighted mean complete response (platelet count $\geq 100 \times 10^9$/L) and overall response (platelet count $\geq 30 \times 10^9$/L and at least doubling of the basal count) were 42.7% (95% confidence interval [CI], 31.8%-53.9%) and 50.3% (95% CI, 41.6%-59.0%), respectively. In 222 patients with a baseline platelet count less than 30×10^9/L, the complete response rate was 20.1% (95% CI, 13.5%-26.7%) and the overall response rate was 35.2% (95% CI, 28.0%-42.4%). The response rate tended to be higher in countries with a high background prevalence of *H pylori* infection and in patients with milder degrees of thrombocytopenia. These findings suggest that the detection and eradication of *H pylori* infection should be considered in the work-up of patients with seemingly typical ITP. (Blood. 2009;113:1231-1240)

Pays à haute prévalence H Pylori
Thrombopénie modérée

Toute thrombopénie n'est pas obligatoirement PTI:

Table 3 Isolated Thrombocytopenia: When a Low Platelet Count Does Not Mean ITP[a]

- **Pseudothrombocytopenia (platelet clumping)**
  - Laboratory artifact
  - Type 2B VWD
- **Congenital thrombocytopenias**
  - Large/giant platelets (MPV >11 fL)
    - MYH9-related thrombocytopenia
    - Bernard-Soulier syndrome
    - Gray platelet syndrome
    - Velocardiofacial/DiGeorge syndrome
    - Paris-Trousseau thrombocytopenia/Jacobsen syndrome
  - Normal sized platelets (MPV 7–11 fL)
    - CAMT
    - TAR syndrome
    - Thrombocytopenia and radial synostosis
    - Familial platelet disorder/acute myeloid leukemia
  - Small platelets (MPV < 7 fL)
    - Wiskott-Aldrich syndrome
    - X-linked thrombocytopenia[b]
- **Miscellaneous**
  - Splenomegaly
  - Storage disorders, e.g., Gaucher disease

Quand mettre en doute le diagnostic?

- Age jeune enfant (< 12-18 mois)
- Découverte systématique
- Eléments cliniques discordants :
  - absence ou gravité du syndrome hémorragique
  - présence d'une splénomégalie
  - symptômes et anomalies associés
- Atteinte d'une autre lignée à la 1ère NFS
- Thrombopénie modérée > 50 G/L
- Caractère réfractaire d'emblée

4 - POSSIBILITÉS THÉRAPEUTIQUES

Possibilités thérapeutiques

1. **Abstention**
2. Corticoïdes
3. Immunoglobulines
4. Anti Rh D
5. Splénectomie
6. Anti CD 20
7. Les analogues de la thrombopoeitine
8. Immunosupresseurs

« Traiter ou ne pas traiter.. »

“L’art de la médecine consiste à distraire le malade pendant que la nature le guérit”.

Voltaire

La vie est dangereuse; la preuve..
Personne n'en sort vivant!

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

Table 8. Grade of severity and management of patients with ITP

Bleeding/quality of life	Management approach
Grade 1. Minor bleeding, few petechiae (≤ 100 total) and/or ≤ 5 small bruises (≤ 3-cm diameter); no mucosal bleeding	Consent for observation
Grade 2. Mild bleeding, many petechiae (> 100 total) and/or > 5 large bruises (> 3-cm diameter); no mucosal bleeding	Consent for observation or for treatment in selected children
Grade 3. Moderate bleeding, overt mucosal bleeding, troublesome lifestyle	Intervention to reach grade 1/2 in selected children
Grade 4. Mucosal bleeding or suspected internal hemorrhage	Intervention

Modified from Buchanan and Adix[181]; Bolton-Maggs and Moon[174]; Imbach et al.[171]

Provan D, Blood 2010

Autres facteurs influençant la décision

1. L'âge de l'enfant
2. Impact sur la qualité de vie
3. L'anxiété des parents
4. L'anxiété du médecin

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5. Le coût +++

ITP et qualité de vie

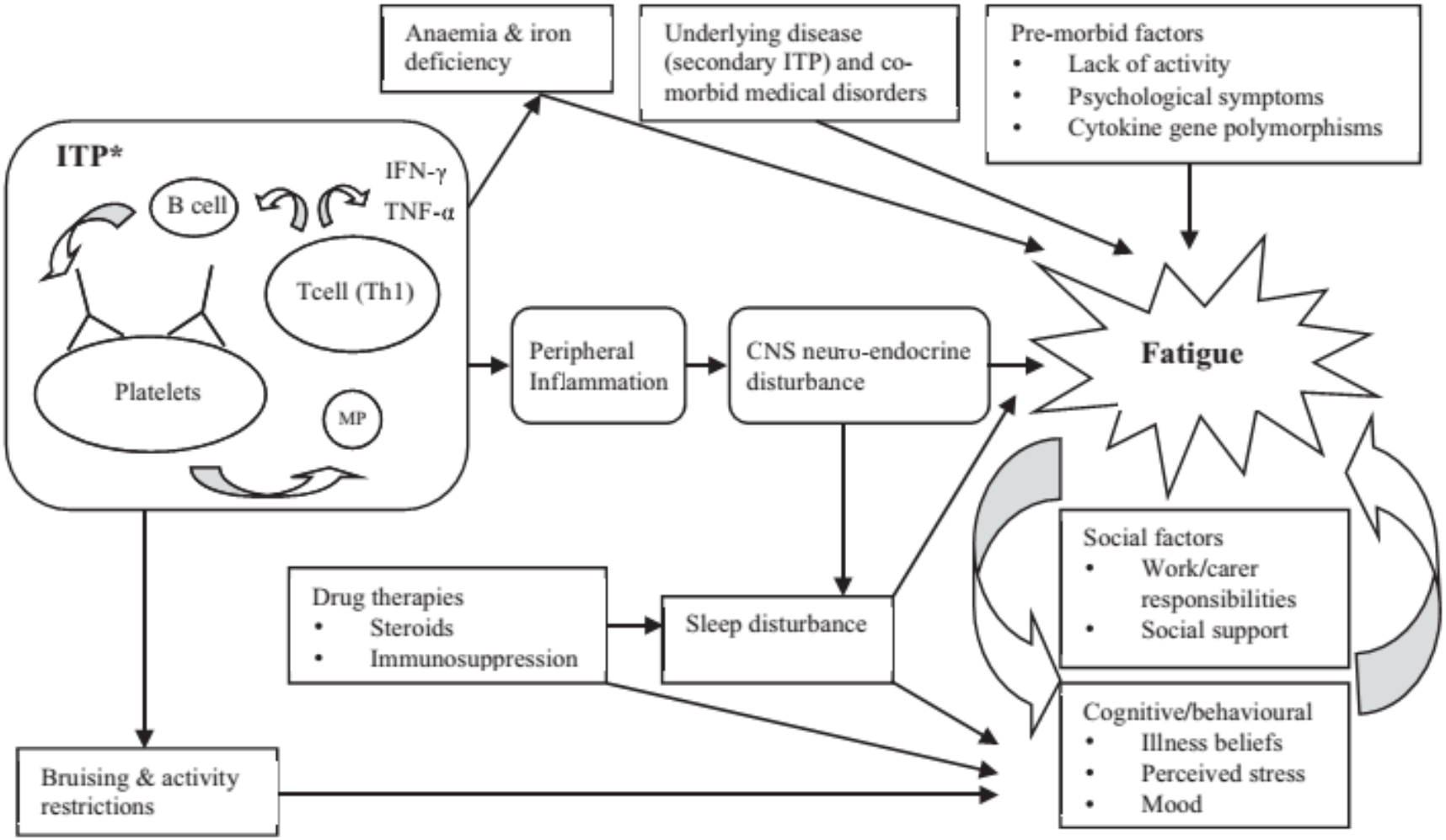
Fatigue in immune thrombocytopenia

British Journal of Haematology, 2015, **170,** 141–149

Summary

Fatigue is an important aspect of health-related quality of life from the patient perspective and can have significant socio-economic consequences. It is a common feature of chronic illnesses and a significant number of both adults and children with immune thrombocytopenia (ITP) suffer from fatigue. Reliable, validated fatigue scales have been developed for use in ITP. These will facilitate future investigation of its pathogenesis and the effectiveness of intervention. Acute inflammation acts on neural and endocrine systems resulting in 'sickness behaviour', an adaptive response to infection and injury. Inflammation is also thought to cause fatigue in chronic disease and immune dysregulation in ITP appears to have a number of pro-inflammatory components. Clinicians should consider fatigue when assessing the burden of disease. Although effective ITP-directed therapy can improve fatigue, a number of fatigue-directed strategies may also need to be considered.

- Blatt et al en 2010 → fatigue dans 22% des enfants ont rapporté une fatigue
- Dysregulation immune → impact neuroendocrinien
- Traitement ITP → reduction de la fatigue
- Autres drogues à considere:
  - Mélatonine
  - Thyrotropine releasing hormone
  - Dopaminergiques ..


Anaemia & iron deficiency
Underlying disease (secondary ITP) and co-morbid medical disorders
Pre-morbid factors
• Lack of activity
• Psychological symptoms
• Cytokine gene polymorphisms
ITP*
IFN-γ
TNF-α
B cell
Tcell (Th1)
Platelets
MP
Peripheral Inflammation
CNS neuro-endocrine disturbance
Fatigue
Social factors
• Work/carer responsibilities
• Social support
Drug therapies
• Steroids
• Immunosuppression
Sleep disturbance
Cognitive/behavioural
• Illness beliefs
• Perceived stress
• Mood
Bruising & activity restrictions

Thrombopénie Immune « aigue »

Nouvellement diagnostiqué

Trois possibilités thérapeutiques

1. Prednisone 4mg/Kg/jour x 4jours
2. Immunoglobulines 0.8 g/Kg une seule dose
3. Les anti Rh-D 75 µg/Kg chez les patients Rh+

CORTICOSTEROIDS VERSUS INTRAVENOUS IMMUNE GLOBULIN FOR THE TREATMENT OF ACUTE IMMUNE THROMBOCYTOPENIC PURPURA IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

CAROLYN E. BECK, MD, MSc, FRCPC, PAUL C. NATHAN, MD, MSc, FRCPC, PATRICIA C. PARKIN, MD, FRCPC, VICTOR S. BLANCHETTE, MB, BChir, FRCPC, AND COLIN MACARTHUR, MBChB, PhD

Objective To compare the effectiveness of corticosteroids with intravenous immune globulin (IVIG) for the initial treatment of children with acute immune thrombocytopenic purpura (ITP).

Study design A systematic review and meta-analysis of randomized controlled trials comparing corticosteroids with IVIG. Studies were identified from eight electronic databases, meeting abstracts, expert consultation, and hand-searched reference lists. Two authors independently reviewed potentially eligible studies and extracted data. The number of patients with a platelet count >20,000/mm^3, 48 hours after treatment initiation, was the primary outcome. Relative risks (RR) and risk differences were pooled using a random effects model, and numbers needed to treat (NNT) were calculated.

Results A total of 1248 abstracts were reviewed, 55 articles were retrieved, and 10 studies were included. The RR (steroids vs IVIG) of achieving a platelet count >20,000/mm^3 at 48 hours was 0.74 (95% CI: 0.65, 0.85), and the NNT was 4.55 (95% CI: 3.23, 7.69).

Conclusion Children treated with corticosteroids for acute ITP are 26% less likely to have a platelet count >20,000/mm^3 after 48 hours of therapy, when compared with children treated with IVIG. Given the importance of low platelets in the pathogenesis of intracranial hemorrhage (ICH), this difference may hold important clinical implications. ***(J Pediatr 2005;147:521-7)***

CORTICOSTEROIDS VERSUS INTRAVENOUS IMMUNE GLOBULIN FOR THE TREATMENT OF ACUTE IMMUNE THROMBOCYTOPENIC PURPURA IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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- 1248 abstracts
- 55 articles
- 10 études
- Essais randomisés
- Age: 3 mois – 18 ans
- PTI aigu
- Evaluation de :
  - End point primaire: Taux de plaquettes > 20.000 à H48
  - End point secondaires:
    - Taux de plaquettes > 20.000 à H24 et H72
    - Nombre de patients développant un PTI chronique
    - Nombre de HIC
    - Mortalité

J Pediatr, 2005,147: 521-7

Conclusion

Un PTI traité par corticoïdes à 26% moins de chances d'avoir un taux de plaquettes > 20 000 dans les 48 h

blood

2011 117: 4190-4207
Prepublished online February 16, 2011;
doi:10.1182/blood-2010-08-302984

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

Cindy Neunert, Wendy Lim, Mark Crowther, Alan Cohen, Lawrence Solberg, Jr and Mark A. Crowther

Initial management of ITP

1.2.A. We recommend:

- Children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) be managed with observation alone regardless of platelet count (grade 1B).

Initial pharmacologic management of pediatric ITP

1.3.A. We recommend:

- For pediatric patients requiring treatment, a single dose of IVIg (0.8-1 g/kg) or a short course of corticosteroids be used as first-line treatment (grade 1B).
- IVIg can be used if a more rapid increase in the platelet count is desired (grade 1B).
- Anti-D therapy is not advised in children with a hemoglobin concentration that is decreased due to bleeding, or with evidence of autoimmune hemolysis (grade 1C).

1.3.B. We suggest:

- A single dose of anti-D can be used as first-line treatment in Rh-positive, nonsplenectomized children requiring treatment (grade 2B).

Immunoglobulines si nécessité d'une augmentation rapide du taux de plaquettes

Table 3. Individual agents for treatment of ITP and the time to the first and peak responses if using the reported dose range

Agent/treatment	Reported dose range	Time to initial response*	Time to peak response*
Prednisone[4,44]	1-4 mg/kg po daily × 1-4 wk	4-14 d	7-28 d
Dexamethasone[48,49]	40 mg po or iv daily × 4 d for 4-6 courses every 14-28 d	2-14 d	4-28 d
IVIg[41,46,50]	0.4-1 g/kg per dose iv (1-5 doses)	1-3 d	2-7 d
Anti-D[42,47]	75 μg/kg per dose iv	1-3 d	3-7 d
Rituximab[10,40,51]	375 mg/m^2 per dose iv (4 weekly doses)	7-56 d	14-180 d
Splenectomy[43]	Laparoscopic	1-56 d	7-56 d
Vincristine[4]	up to 2 mg/dose iv (4-6 weekly doses)	7-14 d	7-42 d
Vinblastine[4,45]	0.1 mg/kg per dose iv (6 weekly doses)	7-14 d	7-42 d
Danazol[4,52]	400-800 mg po daily	14-90 d	28-180 d
Azathioprine[52]	2 mg/kg po daily	30-90 d	30-180 d
AMG531[6,7,9]	3-10 μg/kg weekly sc	5-14 d	14-60 d
Eltrombopag[8]	50-75 mg po daily	7-28 d	14-90 d

Neunert, Blood, 2011: 4190 - 4207

Efficacy of combined intravenous immunoglobulins and steroids in children with primary immune thrombocytopenia and persistent bleeding symptoms

*Blood Transfus 2014; **12**: 340-5*

Background. The aim of this study was to investigate the effect of the combined administration of intravenous immunoglobulins and steroids as a second-line therapy in 34 children with primary immune thrombocytopenia and persistent, symptomatic bleeding.

Materials and methods. Combined therapy (intravenous immunoglobulins 0.4 g/kg daily on days 1 and 2, and methylprednisolone 20 mg/kg daily on days 1-3) was administered to 12 patients with newly diagnosed ITP who did not respond to the administration of a single therapy (either intravenous immunoglobulins or steroids) and to 22 children with persistent and chronic disease who required frequent administrations (i.e. more frequently than every 30 days) of either immunoglobulins or steroids (at the same standard dosages) in order to control active bleeding.

Results. A response (i.e. platelet count $>50\times10^9$/L and remission of active bleeding) was observed in 8/12 (67%) patients with newly diagnosed ITP. The clinical presentation of responders and non-responders did not differ apparently. Patients in the chronic/persistent phase of disease had a significantly longer median period of remission from symptoms compared with the previous longest period of remission ($p=0.016$). The treatment was well tolerated.

Discussion. Our data suggest that the combined approach described is a well-tolerated therapeutic option for children with primary immune thrombocytopenia and persistent bleeding symptoms that can be used in both emergency and/or maintenance settings.

Thrombopénie immune chronique

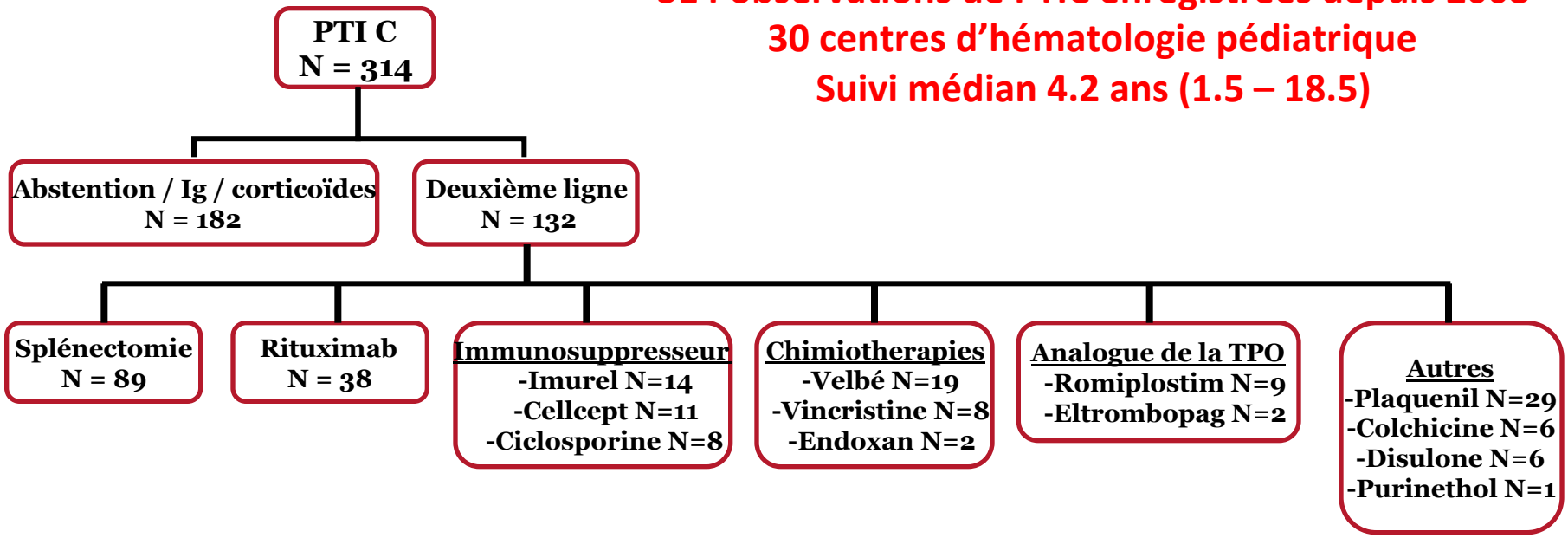
Alternatives thérapeutiques

1. **Corticoides, Immunoglobulines et anti D**
2. **Splénectomie**
3. **RITUXIMAB**
4. **Immunosuppresseurs**
5. **Analogues de récepteurs TPO**
6. **Immuno-supresseurs**

Traitement des PTI chroniques de l'enfant

Etat des lieux des pratiques Mars 2011

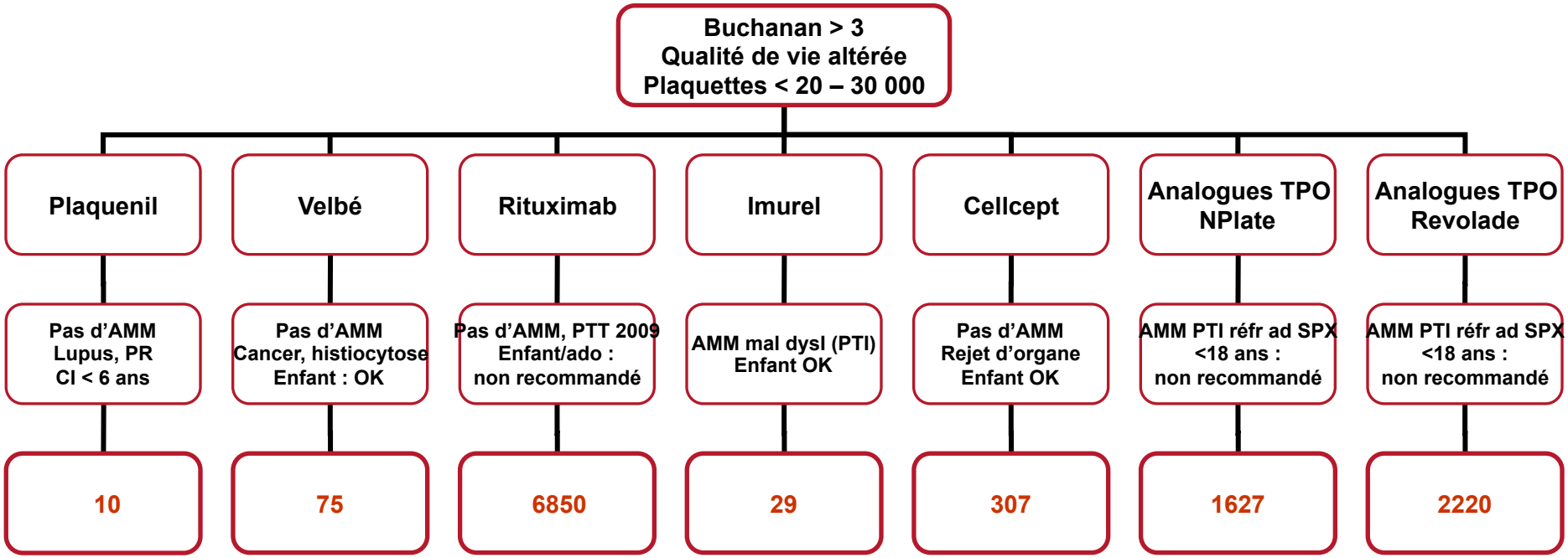
314 observations de PTIC enregistrées depuis 2008
30 centres d'hématologie pédiatrique
Suivi médian 4.2 ans (1.5 – 18.5)



Données rétrospectives non exhaustives +++
1995-2011, en moyenne 15-20 enfants / an ont besoin d'un ttt de 2ème ligne

Diapo G Leverger

Traitement des PTI persistants ou chroniques de l'enfant



Coût en euro pour 1 mois de traitement pour un adulte de 1.73 m^2

Diapo G Leverger

1 - La splénectomie

- 70 à 80% de rémission
- Seuls **15 – 20%** des PTI chroniques seront splénéctomisés
- Pas de facteur prédictifs de réponse
- Risque majeur = **sepsis**
  - 1 DCD/ 300 à 1 000 patients
  - Vaccination et antibioprophylaxie
  - Kuhn et Al en 2007

Table 4 CR Rates Following Splenectomy in Children

Author, Reference	Number of Cases	CR (%)
ASH review[3]	271	72
Blanchette et al[63]	21	81
Ben-Yehuda et al[64]	27	67
Mantadakis et al[65]	38	76
Kühne et al[66]	131	69
	488	**71.5 (349/488)**

CR, complete remission.

Breakey Semin Thromb Hemost 2011

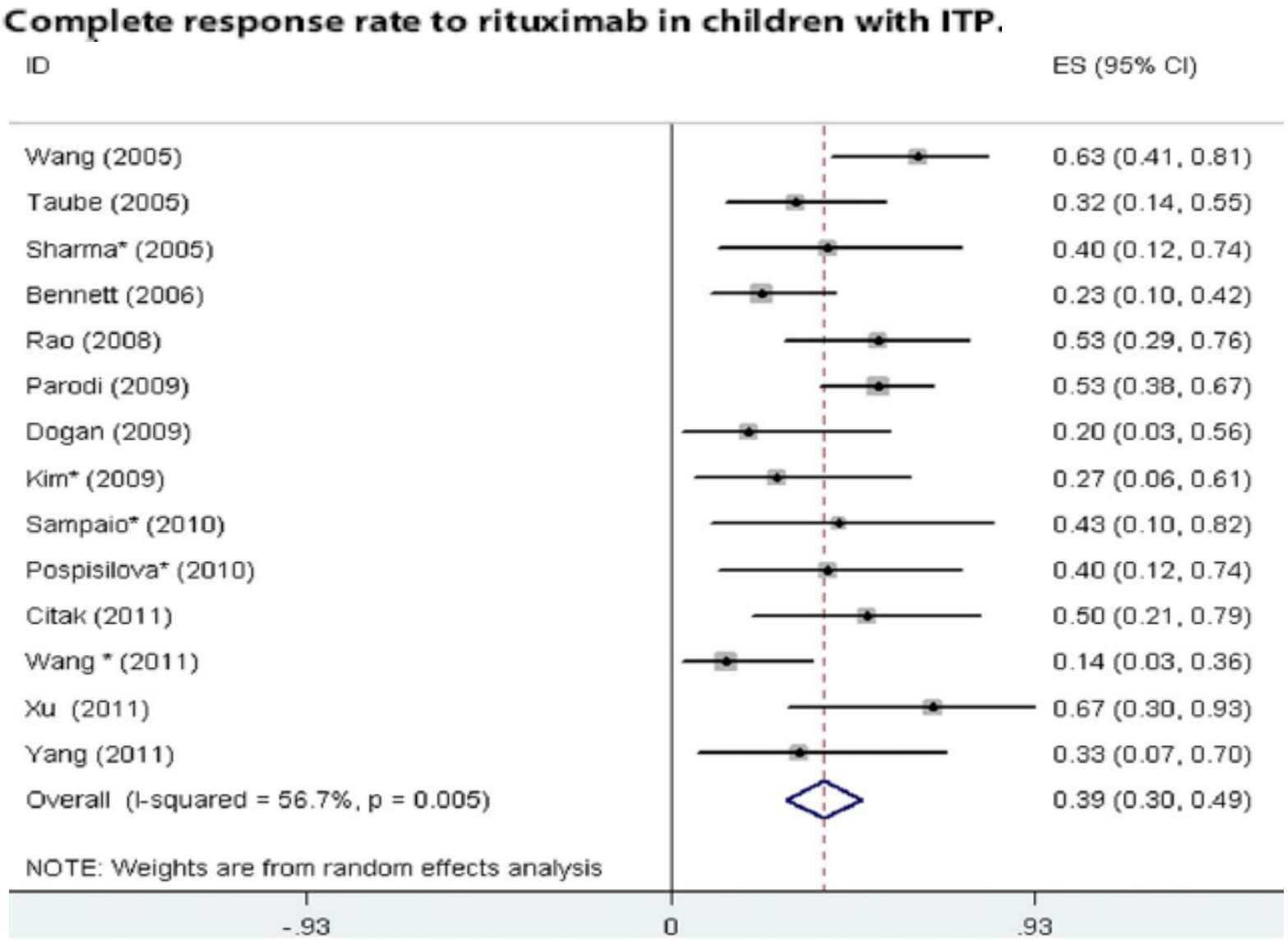
La splénectomie

- ASH guidelines 2007
  - PTI **chronique ou persistant** avec saignement important ou persistant et une absence de réponse ou intolérance aux traitements conventionnels .
  - Recommandé après **12 mois** d'évolution, sauf autre pathologie grave associée ou considérations en rapport avec la qualité de vie.

2 - RITUXIMAB

- Chez l'adulte
  - ~ 50 - 60% de réponse partielle ou complète
  - ~ 28 – 40% de rémission complète
- Chez l'enfant

RITUXIMAB



39%

Liang Y, PLoS One. 2012

Recommandations ASH 2011

Question: What treatments should be considered for children who are unresponsive to initial treatment and/or who have persistent or chronic ITP?

2.1.A. We suggest:

- Rituximab be considered for children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIg, anti-D, or conventional doses of corticosteroids (grade 2C).
- Rituximab may also be considered as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favorably to splenectomy (grade 2C).

3 - Elthrombopag et Romiplastim

Tableau 1 Données galéniques et pharmacologiques des ARTPO.

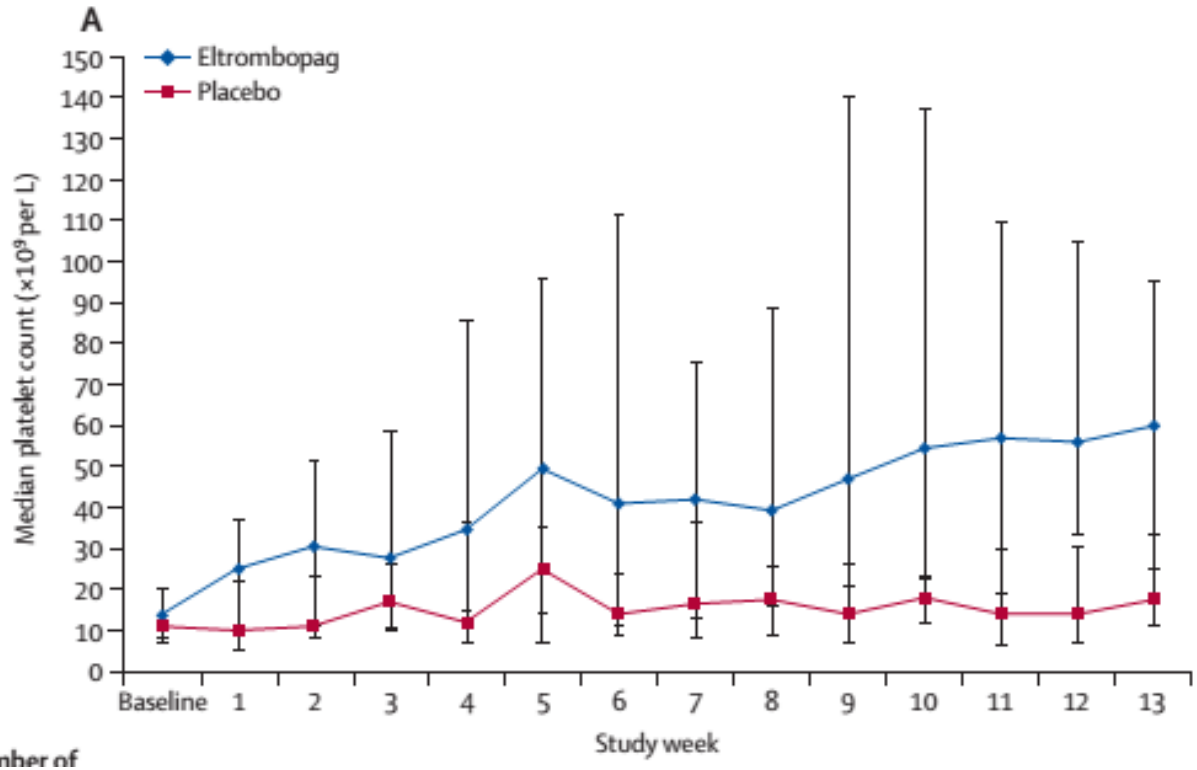
	Romiplostim	Eltrombopag
Dosages	Ampoules pour sous-cutanée de 250 et 500 ug	Comprimés de 12,5, 25 et 50 mg non sécables Pas de suspension buvable
Dilution ou administration	Reconstitution dans 0,7 (ampoule de 250 ug) ou 1,2 mL (ampoule de 500 ug)	Per os Au moins 4 h avant ou après la prise d'anti-acides ou de produits laitiers
Posologie initiale	1 ug/kg/semaine 3 ug/kg/semaine si signes hémorragiques menaçants	Âge 12—17 ans : 50 mg/j (patients d'Asie SE 25 mg/j) Âge 6—11 ans : poids < 27 kg, 12,5 mg ; poids ≥ 27 kg, 25 mg (idem Asie SE). Âge 1—5 ans : 0,7 mg/kg
Adaptation thérapeutique	Augmentation de 1 ug/kg/semaine pour obtention pq > 50 G/L Si pq entre 150 et 400 G/L : dose identique Si pq > 400 G/L : baisser de 1 ug/kg/semaine	Augmentation de 12,5 mg/semaine pour obtention pq > 50 G/L Si pq entre 150 et 400 G/L : dose identique Si pq > 400 G/L, baisser de 12,5 mg/semaine
Dose maximale	10 ug/kg/semaine	75 mg/j
Critères d'arrêt	Absence de réponse clinique et biologique après 4 semaines de traitement à dose maximale	Absence de réponse clinique et biologique après 4 semaines de traitement à dose maximale

Pq : plaquettes.

Pasquet. Journal d'Hématologie et Oncologie Pédiatrique 2015

Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial

Lancet 2015; 386: 1649–58



Number of

Les agonistes des récepteurs TPO

- Brussel et al en 2011
  - 22 patients
  - Étude randomisée en double aveugle
  - 1 à 18 ans
  - ITP > 6 mois
  - 12 doses hebdomadaires (dose médiane 5 µg/kg/j)
  - 88% de réponse dans le bras ROMIPLASTIM vs 0% pour le placebo

Long terme?

Pediatr Blood Cancer 2015;62:208–213

Long-Term Use of the Thrombopoietin-Mimetic Romiplostim in Children With Severe Chronic Immune Thrombocytopenia (ITP)

Background. Treatment of chronic severe pediatric ITP is not well studied. In a phase 1/2 12–16-week study, 15/17 romiplostim-treated patients achieved platelet counts $\geq 50 \times 10^9$/L, and romiplostim treatment was well tolerated. In a subsequent open-label extension ($\leq$109 weeks), 20/22 patients received romiplostim; all achieved platelet counts $>50 \times 10^9$/L. Twelve patients continued in a second extension ($\leq$127 weeks). Longitudinal data from start of romiplostim treatment through the two extensions were evaluated to investigate the safety and efficacy of long-term romiplostim treatment in chronic severe pediatric ITP. ***Procedure.*** Patients received weekly subcutaneous romiplostim, adjusted by 1 μg/kg/week to maintain platelet counts (50–200 $\times 10^9$/L, maximum dose 10 μg/kg). Bone marrow examinations were not required. ***Results.*** At baseline, patients were median age 10.0 years; median ITP duration 2.4 years; median platelet count 13×10^9/L; 73% were male; and 36% had prior splenectomy. Median romiplostim treatment duration was 167 weeks (Q1, Q3: 78,227 weeks), and median average weekly dose was 5.4 μg/kg (Q1, Q3: 4.3, 8.0 μg/kg). Seven patients discontinued treatment: four withdrew consent, two were noncompliant, and one received alternative therapy. None withdrew because of adverse events (AEs). After the first 12 weeks, median platelet counts remained $>50 \times 10^9$/L. Eight (36.4%) patients received rescue medication, and 14 (63.6%) used concurrent ITP therapy. Seven patients (31.8%) reported serious AEs, and two (9.1%) reported life-threatening AEs (both thrombocytopenia); there were no serious AEs attributed to treatment and no fatalities. ***Conclusions.*** Long-term romiplostim treatment in this small cohort increased and maintained platelet counts for over 4 years in children with ITP with good tolerability and without significant toxicity. Pediatr Blood Cancer 2015;62:208–213.

Key words: autoimmunity; bleeding; platelets; thrombopoietin

Recommandations CEREVANCE

1. PTI aigue, persistant ou chronique à syndrome hémorragique sévère mettant en jeux pronostic vital ou fonctionnel
2. PTI Chronique avec score Buchanan > 3 altérant la QOL avec asthénie et taux plaq < 10 000, réfractaire aux corticoides et IG et à au moins une 2ème ligne
3. PTI chronique dans le but de retarder la splénectomie ou en attendant l'efficacité des immunosuppresseurs
4. PTI Chronique en préparation d'un geste chirurgical
5. Exceptionnellement PTI chronique altérant la QOL chez un adolescent ou jeune adulte à une période où le PTI peut altérer l'activité

ITP Adulte vs pediatrique

ITP	In children	In adults
Clinical	Extensive purpura Hemorrhagica (petechiae and hematoma), epistaxis, hematuria, bloody stools, metro- menorrhagia, conjunctival purpura, retinal bleeding, ICH (<0.5%)	
Prevalence	Prevalence of males Bleeding tendency: 90%	Prevalence of females Bleeding tendency: 70%
Diagnostic tools	Increased platelet size, reticulated platelets (Platelet-associated immunoglobulins, IPF) Platelet-associated immunoglobulins (PAIgs), MAIPA	
Spontaneous remission	approx. 80% within one year	Approx. 20-30% within one year
First-line treatment	"Wait and see" (if platelets are >20×10⁹/L) IvIG (if platelets are <20×10⁹/L and mucosal bleeding symptoms)	Corticosteroids IvIG anit-D
Other treatment options	Corticosteroids, anti D, Platelet concentrates and high dose corticosteroids in critical situations	Rituximab
Splenectomy in refractory chronic ITP	Should be avoided in children because of lifelong risk of OPSI syndrome Remission induction rate: 70-80%	Remission induction rate: approx. 65%
Thrombomimetics	First studies published	Approved for chronic ITP

Schulz e. Hematologica 2011

En conclusion

- Pathologie **« non maligne »**
- Spontanément résolutive le plus souvent
- Retentissement sur la qualité de vie (anxiété, fatigue)
- Plusieurs possibilités thérapeutiques mais ..
- Nécessité de facteurs **PREDICTIFS**