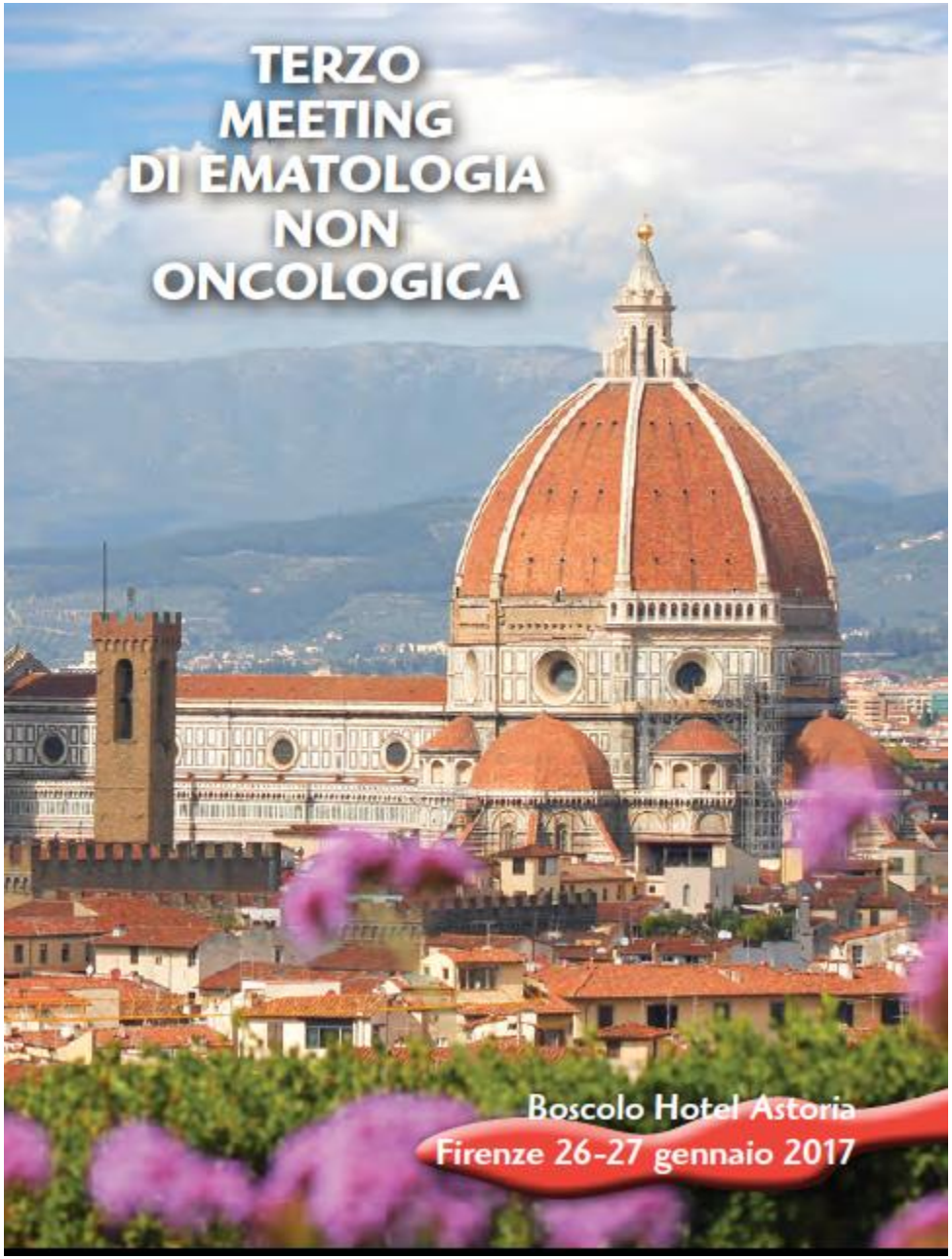


# *Il bridging con TPO-mimetici nella chirurgia*

***Elena Rossi***

**Istituto di Ematologia,**
**Policlinico A. Gemelli**
**Università Cattolica, Roma**

# Outlines

- Preoperative strategies in patients with ITP
- TPO-receptor agonists as preoperative treatment
- Study cases

**Recommendations for first line therapy in adults:**

There are no randomized studies comparing no treatment vs. therapy with corticosteroids or IVIg. There is no indication for therapy in adults in whom there are no symptoms or signs, or in whom the platelet count is greater than $30 \times 10^9/l$ (Grade C recommendation). IVIg is useful in 75% of patients in whom the platelet count has to be raised either due to symptoms or signs, or where there is predictable bleeding (e.g. surgery, pregnancy/labour or operative dentistry).

**Recommendation for "safe" platelet counts in adults**

Dentistry $\geq 10 \times 10^9/l$
Extractions $\geq 30 \times 10^9/l$
Regional dental block $\geq 30 \times 10^9/l$
Minor surgery $\geq 50 \times 10^9/l$
Major surgery $\geq 80 \times 10^9/l$
Obstetrics see *Thrombocytopenia in pregnancy*
Evidence Level IV

***Br J Haematol 2003***

**Recommendation box 2**

| **Consensus-based recommendation for target platelet counts during surgery in adults:*,^** | |
|---|---|
| (Evidence level IV) | |
| Dental prophylaxis (descaling, deep cleaning) | ≥20–30 × $10^9$/L |
| Simple extractions | ≥30 × $10^9$/L |
| Complex extractions | ≥50 × $10^9$/L |
| Regional dental block | ≥30 × $10^9$/L |
| Minor surgery | ≥50 × $10^9$/L |
| Major surgery | ≥80 × $10^9$/L |
| Major neurosurgery | ≥100 × $10^9$/L |
| Splenectomy | see Splenectomy section |
| Obstetrics | see Thrombocytopenia in pregnancy |

***Adult patients considered to be at 'typical' bleeding risk from surgery.[23] Target platelet count depends on the clinical situation and urgency and need for procedure**

**^Concomitant use of antifibrinolytics immediately prior to the procedure may be helpful (see Emergency treatment section)**

Obstetric anesthetists generally recommend a platelet count of at least 75x 10^9/L to allow administration of spinal or epidural anesthesia. Hematologists believe that a platelet count of at least 50x10^9/L is adequate to allow for cesarean section.

***Provan et al, Blood 2009 (Appendix)***

# Preoperative strategies in ITP

- High-dose Intravenous Immunoglobulin
- Platelet  transfusions
- Dexamethasone
- Thrombopoietin receptor agonists

Clinical & Experimental Immunology
The Journal of Translational Immunology

Clinical and Experimental Immunology REVIEW ARTICLE doi:10.1111/j.1365-2249.2011.04389.x

# The experience of Flebogammadif® in primary immune thrombocytopenia

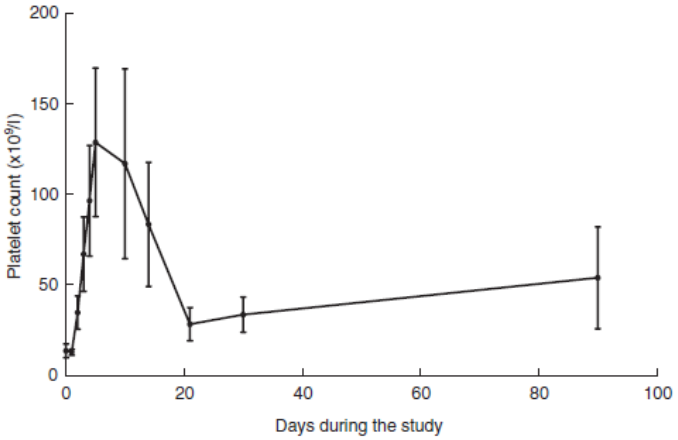


**Fig. 1.** Platelet counts for all patients who received at least one dose of Flebogammadif® (mean values and standard error bars). Values on day 0 indicate platelet count before the first infusion of the study product.

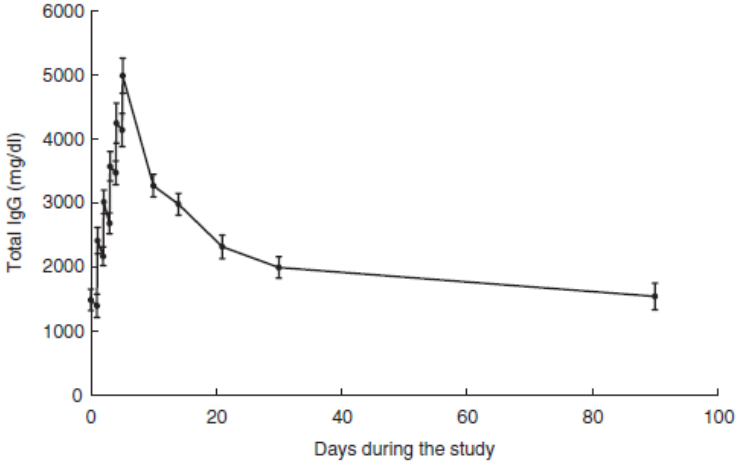


**Fig. 2.** Immunoglobulin G (IgG) levels for all patients who received at least one dose of Flebogammadif® (mean values and standard error bars). Values on day 0 indicate levels of IgG before the first infusion of study product.

**Case Report**

Knee Surg Relat Res 2012;24(4):245-248
http://dx.doi.org/10.5792/ksrr.2012.24.4.245
pISSN 2234-0726 · eISSN 2234-2451

KSRR
Knee Surgery & Related Research

# Perioperative Care of a Patient with Refractory Idiopathic Thrombocytopenic Purpura Undergoing Total Knee Arthroplasty

Rohit Singhal, MS (Ortho), MRCSEd[1], Veera Gudimetla, FRCA[2], Andrew Stewart, FRCP Edin, FRCPath[3], Karen L Luscombe, FRCS (Tr & Orth)[1] and Charalambos P Charalambous, MSc, MD, FRCS (Tr & Orth)[4]

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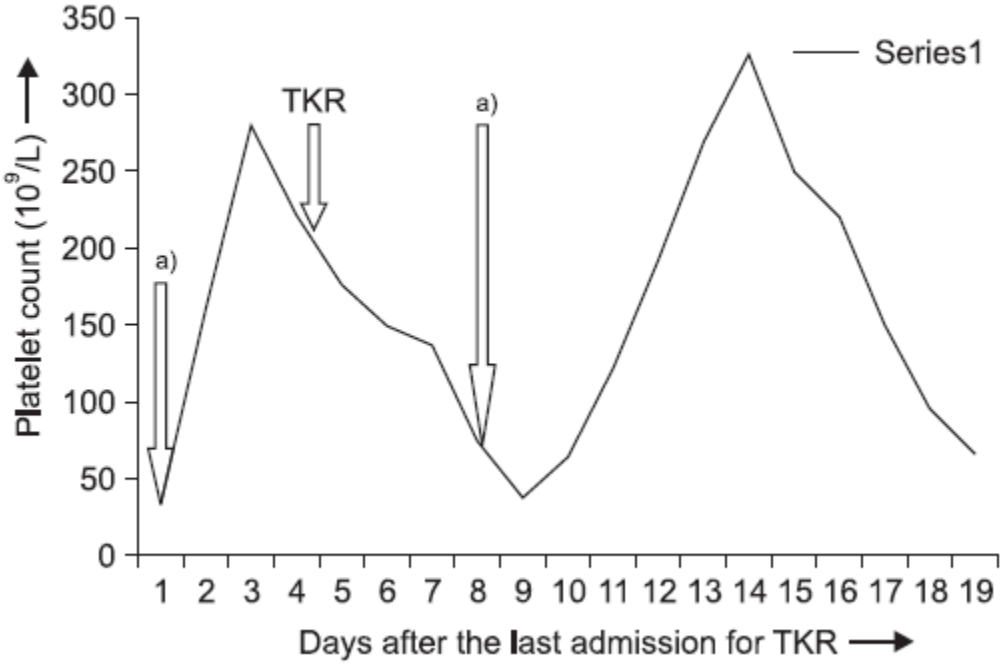
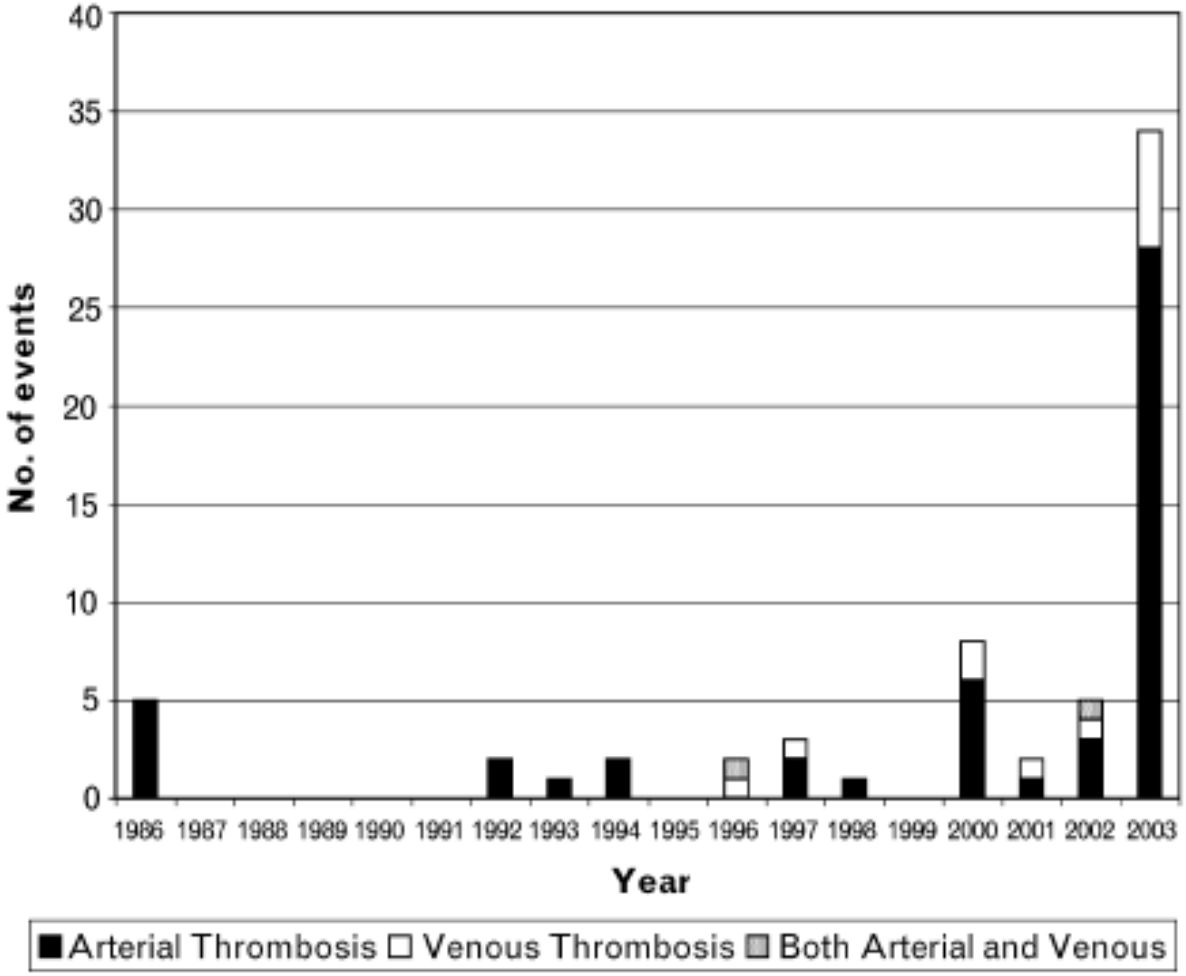


**Fig. 1**


40
35
30
25
20
15
10
5
0
No. of events
1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003
Year
Arterial Thrombosis
Venous Thrombosis
Both Arterial and Venous

# HD-Ig and thrombosis

- A review of the literature revealed 65 reported cases. The incidence rate was estimated at 0.15–1.2% per treatment course.

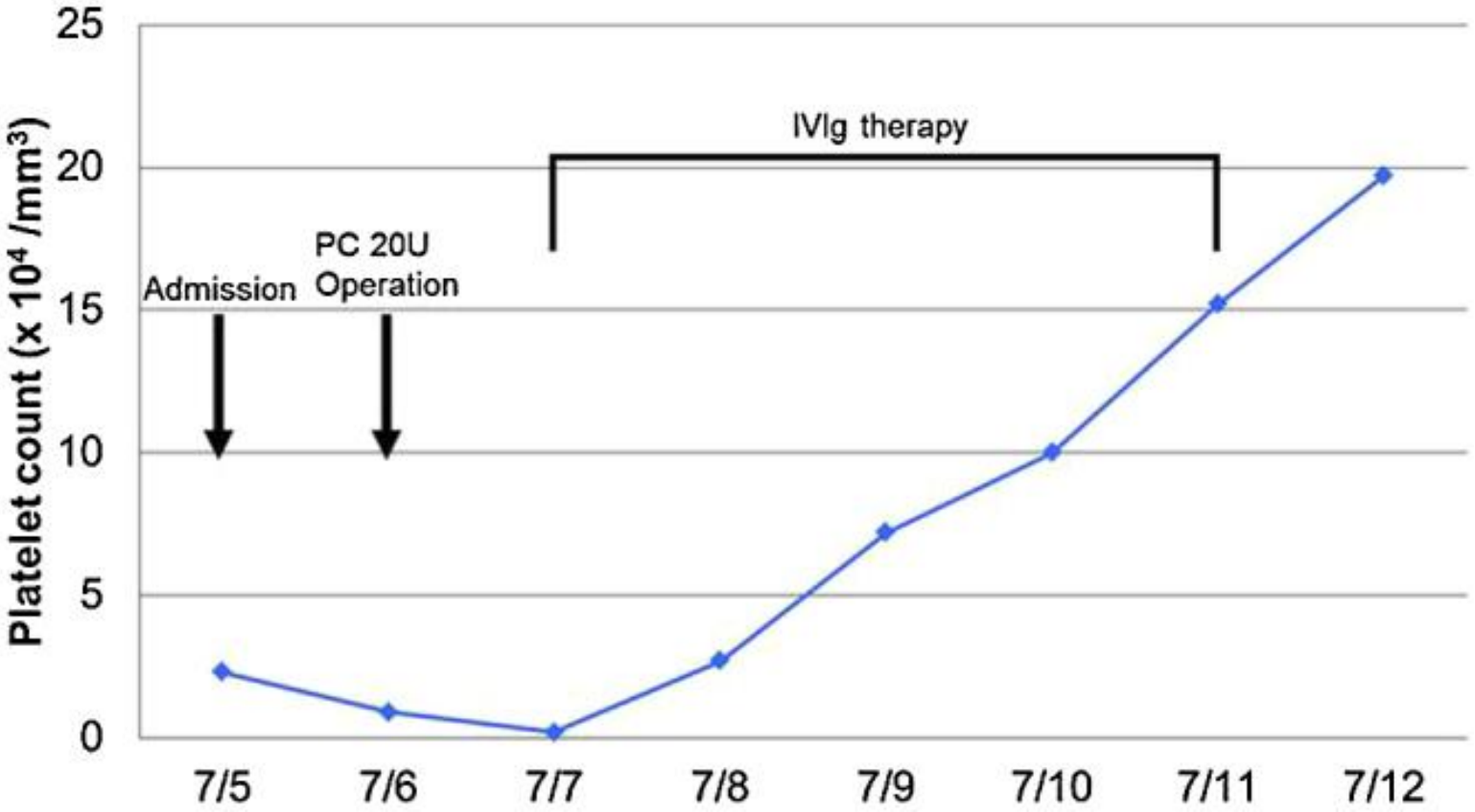
- Arterial thrombosis occurred early after IVIg administration (49% within 4 h, 77% within 24 h) and was associated with advanced age and atherosclerotic vascular disease.

- Venous thrombosis occurred later (54% more than 24 h after IVIg administration) and was associated with factors contributing to venous stasis (obesity and immobility).

*Blood Coag Fibrinolys 2005*

**PRESENTATION OF CASE**

we report the case of a 66-year-old woman with ITP who required an emergency operation for acute appendicitis associated with disseminated intravascular coagulation. Preoperative therapy consisted of platelet transfusions only, and intraoperative hemostasis was achieved. Postoperatively, high-dose intravenous immunoglobulin (IVIg) therapy led to an increased, stable, and adequate platelet count and good hemostasis.




***Toyomasu et al, Int J Surg Case Rep. 2013***

# Platelet transfusions

*Intraoperative platelet support.* There is a suggestion, with little evidence, that if random donor platelets are deemed necessary to cover the surgery, these should be given once the splenic artery has been clamped. Physiologically this would appear logical but has never been subjected to rigorous study (Level IV evidence).

***Br J Haematol 2003***

Journal of Surgical Research 170, e225–e232 (2011)
doi:10.1016/j.jss.2011.06.031

# Laparoscopic Splenectomy for Patients with Immune Thrombocytopenia and Very Low Platelet Count: Is Platelet Transfusion Necessary?

Xiaodong Chen, M.D., Ph.D.,* Bing Peng, M.D., Ph.D.,†,[1] Yunqiang Cai, M.D.,† Jin Zhou, MD,* Yichao Wang, M.D.,† Zhong Wu, M.D.,† and Sirui Chen, M.D.†

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**TABLE 1**

**Patients' Characteristics (mean ± SD, range)**

| | Group Ia $<10 \times 10^9$/L with PT | Group Ib $<10 \times 10^9$/L without PT | Group II $10\text{-}30 \times 10^9$/L without PT | Group III $\geq 30 \times 10^9$/L without PT | *P* value | |
|---|---|---|---|---|---|---|
| | | | | | Ib vs. Ia | Ib vs. II, III |
| Patients, *n* (p/s ITP) | 10 (8/2) | 20 (19/1) | 24 (22/2) | 27 (24/3) | 0.251 | 0.873 |
| Gender, male/female | 4/6 | 3/17 | 8/16 | 5/22 | 0.181 | 0.355 |
| Age at surgery, y | 30.1 ± 14.6 (15.1–54.0) | 35.6 ± 16.3 (19.4–78.8) | 39.0 ± 15.9 (15.6–78.3) | 35.0 ± 15.3 (13.9–66.9) | 0.372 | 0.629 |
| Disease duration,[†] mo | 30 (6–240) | 26 (2–200) | 24 (1–384) | 30 (2–336) | 0.440[‡] | 0.761[§] |
| Comorbidity, *n* (%) | 3 (30) | 4 (20) | 6 (25) | 6 (22) | 0.657 | 0.939 |
| BMI, $kg/m^2$ | 23.1 ± 3.1 (18.3–27.2) | 23.8 ± 3.7 (17.9–28.5) | 23.3 ± 3.4 (18.8–27.2) | 23.6 ± 4.3 (18.0–29.3) | 0.612 | 0.997 |
| Previous abdominal surgery, *n* (%) | 0 (0) | 2 (10) | 1 (4) | 3 (11) | 0.540 | 0.659 |
| Spleen size[¶], mm | 97.1 ± 3.6 (88–116) | 103.3 ± 9.7 (87–123) | 99.8 ± 11.4 (78–128) | 100.6 ± 18.0 (69–132) | 0.062 | 0.993 |
| Pretreatment, *n* | | | | | | |
| GC treatment alone | 5 | 13 | 12 | 10 | 0.240 | 0.802 |
| GC+IVIg treatments | 2 | 5 | 6 | 8 | | |
| GC+other treatments* | 3 | 1 | 3 | 1 | | |
| PC on admission, $\times 10^9$/L | 5.0 ± 3.6 (1–11) | 6.7 ± 7.5 (0–32) | 17.4 ± 30.0 (0–154) | 24.6 ± 24.1 (1–78) | 0.504 | 0.040 |
| PC before surgery, $\times 10^9$/L | 5.7 ± 3.1 (1–9) | 5.6 ± 2.2 (1–9) | 18.4 ± 6.2 (10–28) | 59.9 ± 27.2 (30–131) | 0.918 | <0.001 |
| HGB before surgery, g/L | 106 ± 20 (78–149) | 110 ± 26 (68–153) | 127 ± 21 (80–160) | 130 ± 19 (90–161) | 0.663 | 0.009 |

p/s ITP = primary/secondary immune thrombocytopenia; BMI = body mass index; GC = glucocorticoids; IVIg = intravenous immunoglobulin; PC = platelet count; HGB = hemoglobin.

[*] Other treatments including danazol, azathioprine, or vincristine treatments.

[†] Value is median (range).

[‡] Mann-Whitney U test.

[§] Kruskal-Wallis H test.

[¶] Longitudinal diameter of spleen by USG. PT, platelet transfusion.

**TABLE 2**

**Operative Outcome**

| | Group Ia $<10 \times 10^9$/L with PT | Group Ib $<10 \times 10^9$/L without PT | Group II $10–30 \times 10^9$/L without PT | Group III $\geq 30 \times 10^9$/L without PT | *P* value | |
|---|---|---|---|---|---|---|
| | | | | | Ib vs. Ia | Ib vs. II, III |
| Operative time, min | 175 ± 42 (105–245) | 166 ± 44 (95–245) | 172 ± 56 (95–315) | 146 ± 44 (90–280) | 0.574 | 0.149 |
| Accessory spleen, *n* (%) | 1 (10) | 3 (15) | 6 (25) | 6 (22) | 1.000 | 0.713 |
| Blood loss,[†] mL | 75 (50–225) | 55 (50–100) | 50 (30–188) | 50 (30–60) | 0.319[‡] | 0.151[§] |
| Drain exudate,[†] mL | 73 (38–300) | 80 (36–235) | 64 (10–173) | 40 (10–70) | 0.791[‡] | 0.151[§] |
| Excessive bleeding, *n* (%) | 1 (10) | 2 (10) | 3 (13) | 1 (4) | 1.000 | 0.566 |
| Conversions, *n* (%) | 1 (10) | 1 (5) | 2 (8) | 0 (0) | 1.000 | 0.380 |
| RBC transfusion, *n* (%) | 3 (30) | 6 (30) | 3 (13) | 2 (8) | 1.000 | 0.113 |
| Complications, *n* (%) | 1 (10) | 1 (5) | 4 (17) | 3 (11) | 1.000 | 0.508 |
| Pancreatic leakage | 0 | 0 | 2 | 0 | | |
| Subphrenic fluid collection | 0 | 0 | 2 (1*) | 3 (1*) | | |
| Other minor complications | 1 | 1 | 0 | 0 | | |
| Postoperative LOH, d | 4.5 ± 1.5 (3–7) | 5.0 ± 1.6 (3–10) | 5.0 ± 1.7 (3–11) | 5.6 ± 4.0 (3–25) | 0.409 | 0.724 |

PT = platelet transfusion; LOH = length of hospitalization.

[*]One patient each in groups II and III suffered subphrenic fluid collection and pneumonia simultaneously.

[†]Values are median (interquartile range).

[‡]Mann-Whitney U test.

[§]Kruskal-Wallis H test.

**TABLE 4**

**Platelet Response**

| Platelet response | Group Ia $<10 \times 10^9$/L with PT | Group Ib $<10 \times 10^9$/L without PT | Group II 10-30 $\times 10^9$/L without PT | Group III $\geq 30 \times 10^9$/L without PT | *P* value |
|---|---|---|---|---|---|
| Platelet count, $\times 10^9$/L | | | | | |
| POD 1 | 89 ± 38 | 73 ± 54 | 84 ± 44 | 107 ± 48 | 0.109 |
| At discharge | 224 ± 111 | 246 ± 146 | 336 ± 170 | 348 ± 212 | 0.086 |
| Response rate, *n* (%) | | | | | |
| CR | 9 (90) | 17 (85) | 22 (92) | 24 (89) | 0.846 |
| R | 1 (10) | 2 (10) | 1 (4) | 3 (11) | |
| NR | – | 1 (5) | 1 (4) | – | |

POD = postoperative day; CR = complete response; R = response; NR = no response.

World J Surg (2014) 38:2267–2272
DOI 10.1007/s00268-014-2560-9

# Should We Routinely Transfuse Platelet for Immune Thrombocytopenia Patients with Platelet Count Less Than $10 \times 10^9$/L Who Underwent Laparoscopic Splenectomy?

Yunqiang Cai · Xubao Liu · Bing Peng

However, whether platelet transfusion should be conducted in patients with low platelet count during LS is still controversial. Platelet transfusion is considered appropriate for patients with platelet counts less than $10 \times 10^9$/L and should be given after the splenic artery has been clamped [19, 20]. After clamping of the splenic artery, the circulating platelet count rapidly increases, even without platelet transfusion. The role of platelet transfusion is doubtful in these patients. Furthermore, platelets are also a scarce resource and many adverse effects are associated with platelet transfusion, such as allergic reactions, fever, renal failure, and thromboembolic complications. There is also no evidence that preoperative platelet transfusions have any use during LS for ITP.

# High-dose Dexamethasone

**Table 1. Univariate Analysis of Clinical and Laboratory Variables Associated with the Outcome at Six Months among the 106 Patients with an Initial Response.***

| Variable | Sustained Response at 6 Mo | Relapse within 6 Mo | P Value |
|---|---|---|---|
| Age (yr) | 46.7±18.2 | 45.8±18.5 | 0.80 |
| Sex (no.) | | | 0.31 |
| Female | 33 | 40 | |
| Male | 20 | 13 | |
| Platelet count (per mm³) | | | |
| Pretreatment | 12,300±11,600 | 13,500±11,800 | 0.63 |
| Day 3 | 46,700±16,500 | 42,100±23,400 | 0.34 |
| Day 10 | 132,600±41,900 | 84,700±37,000 | <0.001 |
| 3 Mo | 185,100±73,400 | 59,100±57,500 | <0.001 |

* Plus–minus values are means ±SD.

***Cheng et al, NEJM 2003***

# Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience

Maria Gabriella Mazzucconi,[1] Paola Fazi,[2] Sayla Bernasconi,[1] Giulio De Rossi,[3] Giuseppe Leone,[4] Luigi Gugliotta,[5] Nicola Vianelli,[6] Giuseppe Avvisati,[7] Francesco Rodeghiero,[8] Angela Amendola,[1] Carlo Baronci,[3] Cecilia Carbone,[9] Stefano Quattrin,[10] Giuseppe Fioritoni,[11] Giulio D'Alfonso,[2] and Franco Mandelli,[1] for the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) Thrombocytopenia Working Party

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**Table 5. GIMEMA multicenter pilot study: platelet count of evaluable patients after the end of the first therapy course**

| | | At least 18 years of age through 70 years of age | At least 2 years of age through 17 years of age | | |
|---|---|---|---|---|---|
| | Total | | Total | Less than 10 | 10 or greater |
| Evaluable patients, n | 90 | 48 | 42 | 32 | 10 |
| Median platelet count at fourth day of the first therapy cycle, $\times 10^9$/L (range) | 92 (2-370) | 87 (2-290) | 99 (7-370) | 98 (7-271) | 110 (28-370) |
| Platelets $> 20 \times 10^9$/L, no. patients (%) | 68/75* (91) | 35/38* (92) | 33/37* (89) | 25/29* (86) | 8/8* (100) |
| Platelets $> 30 \times 10^9$/L, no. patients (%) | 76/90 (84) | 42/48 (87) | 34/42 (81) | 26/32 (81) | 8/10 (80) |
| Platelets $\geq 50 \times 10^9$/L, no. patients (%) | 66/90 (73) | 38/48 (79) | 28/42 (67) | 21/32 (66) | 7/10 (70) |

NA indicates not applicable; NS, not significant.
*Patients with platelet count $\leq 20 \times 10^9$/L at enrollment.

***Blood 2007***

High-dose intravenous immunoglobulin (IV IgG) is currently the treatment of choice for patients with idiopathic thrombocytopenic purpura (ITP) who undergo splenectomy; however, this treatment is extremely expensive.

We report on 13 ITP patients with severe thrombocytopenia (<20 x 10(9)/l) who were prepared for laparoscopic splenectomy with a 4-day oral course of high-dose (40 mg/day) dexamethasone (DEX).

Four patients had an excellent response with platelet counts that increased to above 150 x 10(9)/l. Seven patients had a good response with a platelet count that increased to between 50 and 150 x 10(9)/l (median 121 x 10(9)/l). Two patients were resistant both to DEX and IV IgG.

The operation was uneventful in all the patients, including the 2 who had resistant ITP and were operated on while their platelet count was very low (5 x 10(9)/l). Thus, high-dose DEX, which is an easy, effective and inexpensive treatment, is recommended for the preparation of ITP patients prior to splenectomy.

Bulvik et al, Haemostasis. 1998 Sep-Oct;28(5):256-9.
*High-dose dexamethasone for splenectomy in patients with idiopathic thrombocytopenic purpura.*

.

# Postoperative steroids

Excessive doses of steroids cause adverse effects such as

- postoperative infection,
- gastrointestinal haemorrhage
- delayed wound healing

National Surgical Quality Improvement Program (NSQIP) public use files from 2005 to 2008 were analyzed for preoperative steroid use and postoperative adverse events.
Of 635,265 patients identified, 20,434 (3.2%) used steroids preoperatively.
In the steroids group:
Superficial surgical site infections (SSI) increased from 2.9% to 5% (odds ratio, 1.7).
Deep SSIs increased from 0.8% to 1.8% (odds ratio, 2.3).
Wound dehiscence increased from 0.6% to 2% (odds ratio 3.3)



**Table 2** Percentage occurrence of particular adverse events in the steroid and nonsteroid populations with odds ratios

| Adverse event | Steroid patients, % | Nonsteroid patients, % | Odds ratio | *P* value |
|---|---|---|---|---|
| Superficial SSI | 5.0 | 2.9 | 1.72 | <.001 |
| Deep SSI | 1.8 | .8 | 2.35 | <.001 |
| Organ infection | 3.0 | 1.3 | 2.47 | <.001 |
| Dehiscence | 2.0 | .6 | 3.34 | <.001 |
| Pneumonia | 4.7 | 1.6 | 2.98 | <.001 |
| Re-intubation | 4.0 | 1.4 | 2.98 | <.001 |
| Prolonged intubation | 7.2 | 2.3 | 3.38 | <.001 |
| Pulmonary embolism | .7 | .3 | 2.22 | <.001 |
| Progressive renal insufficiency | .9 | .4 | 2.66 | <.001 |
| Acute renal insufficiency | 1.5 | .5 | 3.21 | <.001 |
| Myocardial infarction | .3 | .2 | 1.90 | <.001 |
| Cardiac arrest | 1.1 | .4 | 2.58 | <.001 |
| Return to operating room | 11.2 | 5.4 | 2.21 | <.001 |
| Death | 6.0 | 1.6 | 3.92 | <.001 |

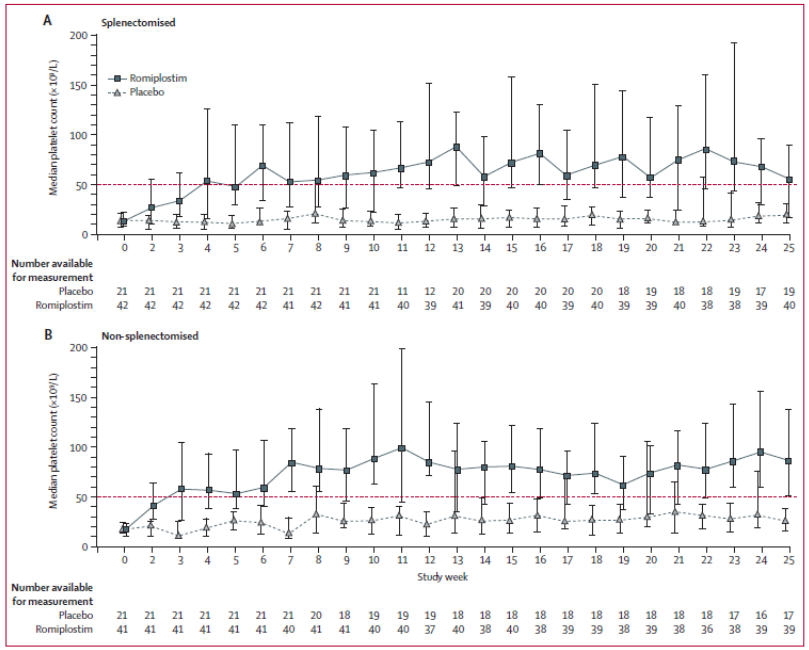
*Am J Surgery 2011*

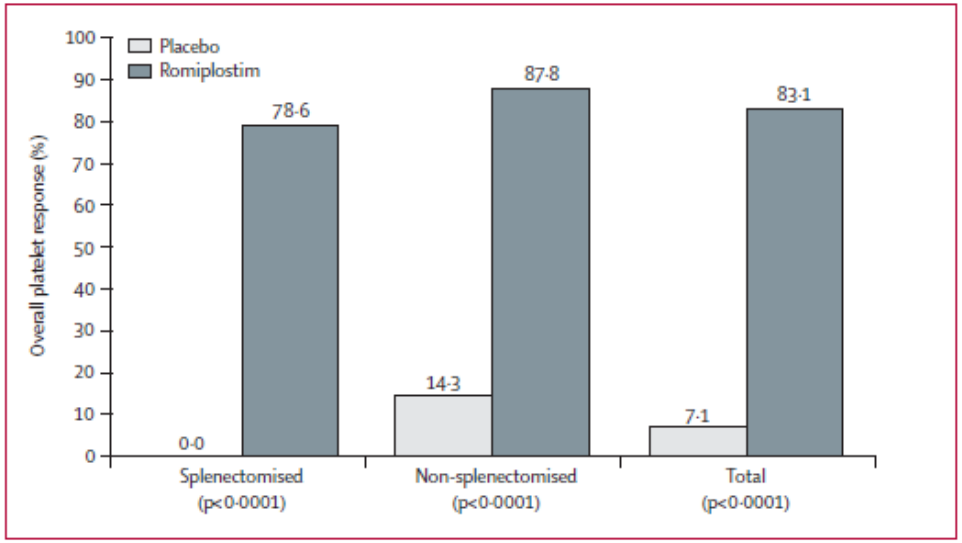
**TABLE 3:**
**Clinical comparisons of patients with abdominal wound dehiscence (AWD) and patients without abdominal wound dehiscence (NAWD)**

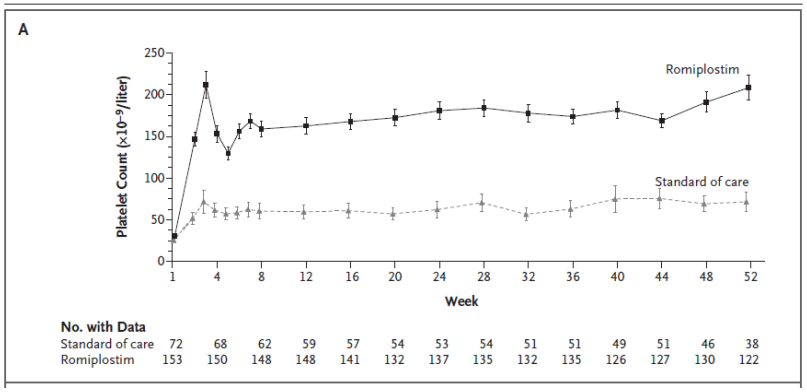
| | AWD ($n = 7$) | NAWD ($n = 21$) | *P*-value |
|---|---|---|---|
| Age (years) | 54.3 ± 12.3 | 47.0 ± 16.0 | NS |
| Gender (male, female) | 1, 6 | 8, 13 | |
| Serum albumin (g/dl) | 2.84 ± 0.39 | 3.05 ± 0.43 | NS |
| Haemoglobin (g/dl) | 11.5 ± 0.87 | 11.3 ± 0.89 | NS |
| Pre-operative total dose of steroid (mg) | 39 755 ± 54 298.4 | 19 130.2 ± 21 810 | NS |
| Duration of steroid administration (months) | 124.3 ± 103.0 | 101.1 ± 115.9 | NS |
| Steroid dose within pre-operative 30 days (mg) | 625.7 ± 383.6 | 645.7 ± 588.3 | NS |
| Post-operative dose of steroid (mg) | 404.3 ± 147.1 | 135.6 ± 118.7 | < 0.001 |
| Duration of wound healing (days) | 57.3 ± 18.0 | 12.4 ± 3.8 | < 0.001 |
| Wound infection | 5 | 7 | NS |

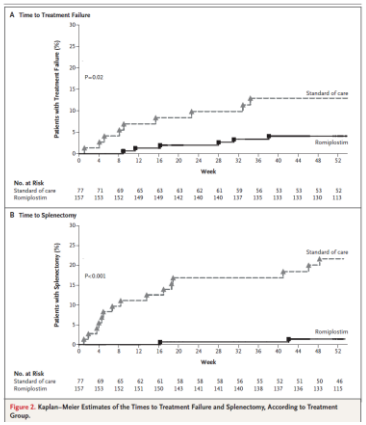
*Kihara et al, J Int Med Res 2006*

# TPO-RECEPTOR AGONISTS



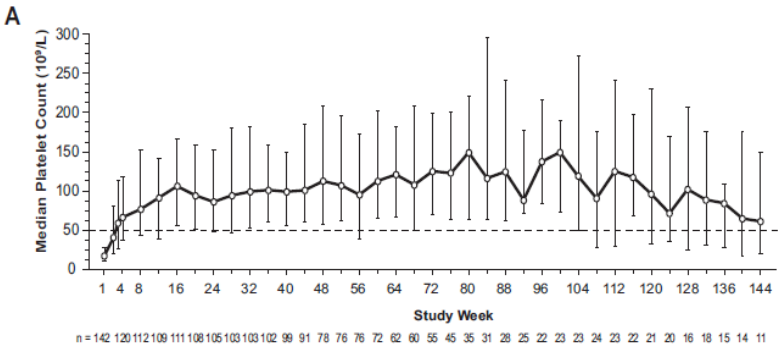



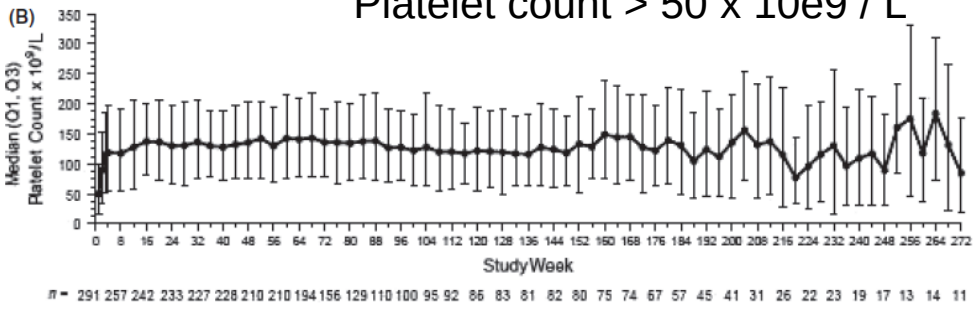



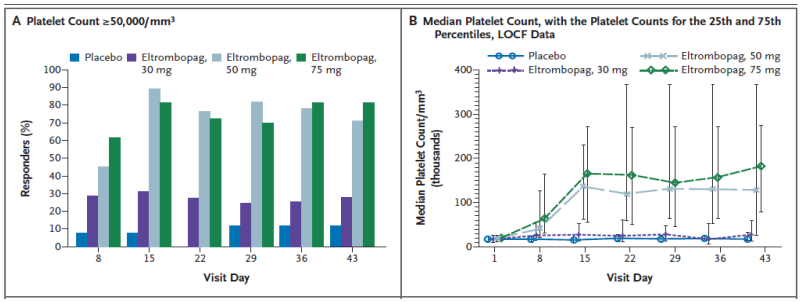

*ROMIPLOSTIM*

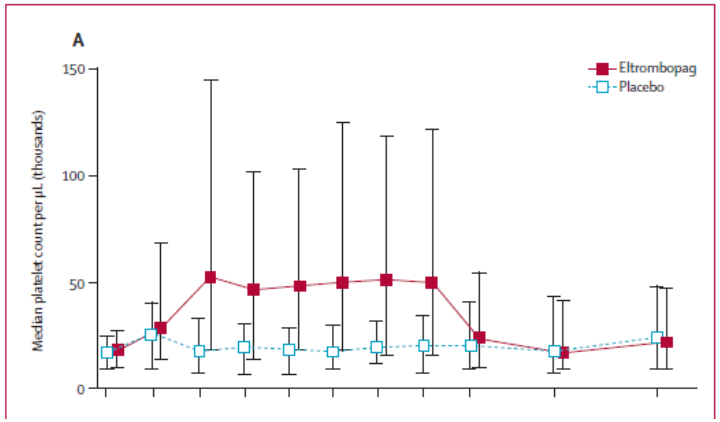
*Kuter et al, Lancet 2008*
*Bussel et al, Blood 2009*
*Kuter et al, NEJM 2010*
*Kuter et al, Br J Hematol 2013*

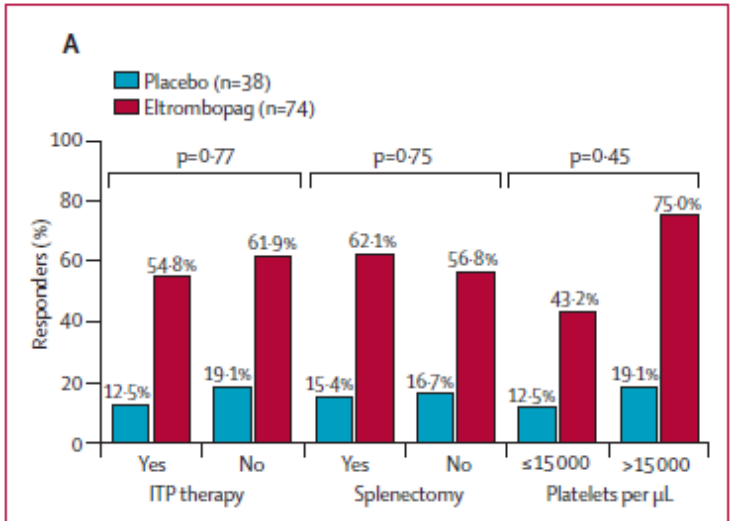
Definition of response:
Platelet count > 50 x 10e9 / L

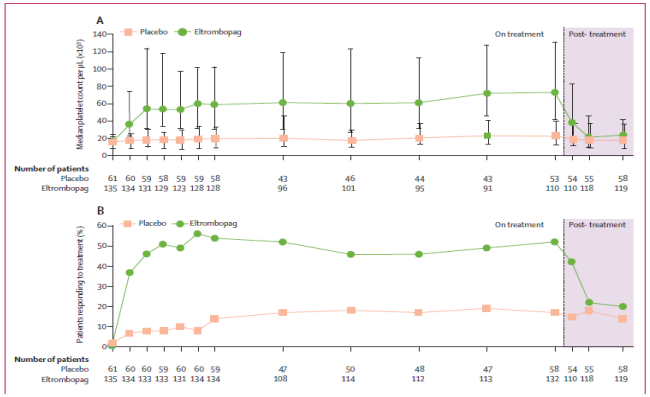


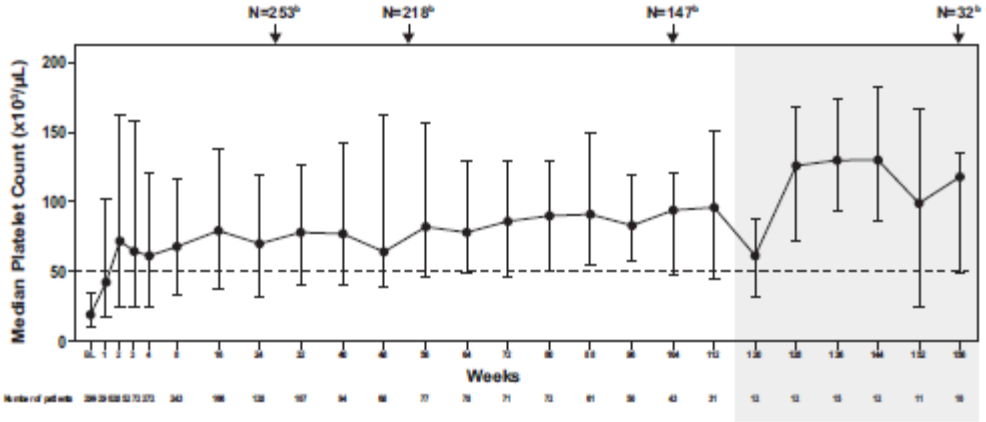






## *ELTROMBOPAG*

*Bussel et al, NEJM 2007*
*Bussel et al, Lancet 2009*
*Cheng et al, Lancet 2011*
*Saleh et al, Blood 2013*

Definition of response:
Platelet count > 50 x 10e9 / L

# Use of the novel thrombopoietin receptor-agonist romiplostim, in combination with steroids and immunoglobulins for the increase of platelets prior to splenectomy, in refractory immune thrombocytopenia: a case report

Piera Sivera[a], Marco Ruella[a,b], Angela Gueli[a,b], Huijing Hu[a], Muhamed Wade[a] and Corrado Tarella[a,b]

**This case report describes a patient with relapsed primary immune thrombocytopenic purpura (ITP), in which splenectomy was not possible due to the persistence of a low platelet count despite treatment with corticosteroids, intravenous immunoglobulins (IVIG) and platelet transfusion treatment. As an attempt to increase platelet count prior to performing splenectomy, the thrombopoietin receptor agonist, romiplostim, was administered in combination with steroids and IVIG. A single administration of romiplostim was found to be markedly effective, allowing a rapid and notable platelet increase, required for a well tolerated splenectomy. This case confirms the potent activity of romiplostim in ITP, and indicates that patients with recurrent primary ITP who are unresponsive to conventional immunosuppressive therapy may benefit from the addition of a short course of romiplostim.** *Blood Coagul Fibrinolysis* **23:331–334** 

**Blood Coagulation and Fibrinolysis** 2012, **23**:331–334

**Keywords: primary immune thrombocytopenia, refractory immune thrombocytopenia, romiplostim, splenectomy, steroids**

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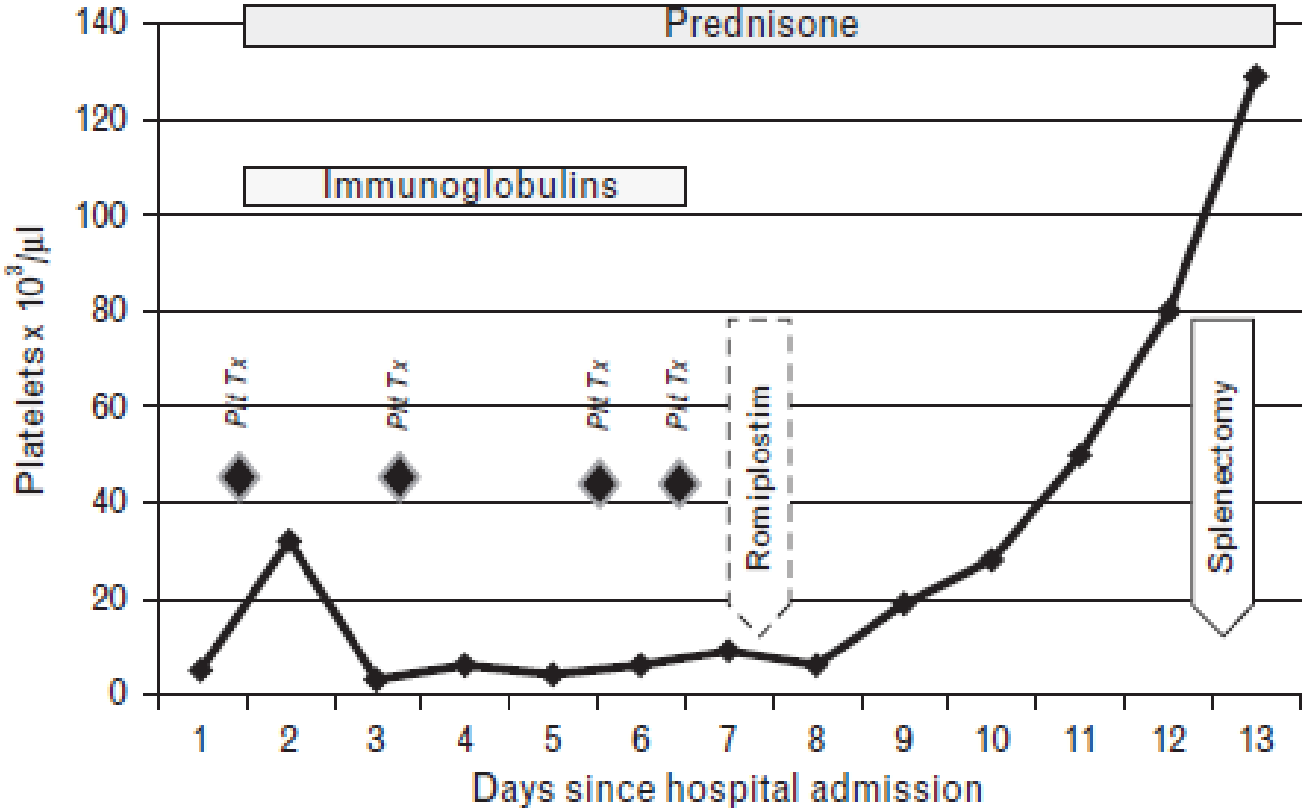
**Fig. 1**

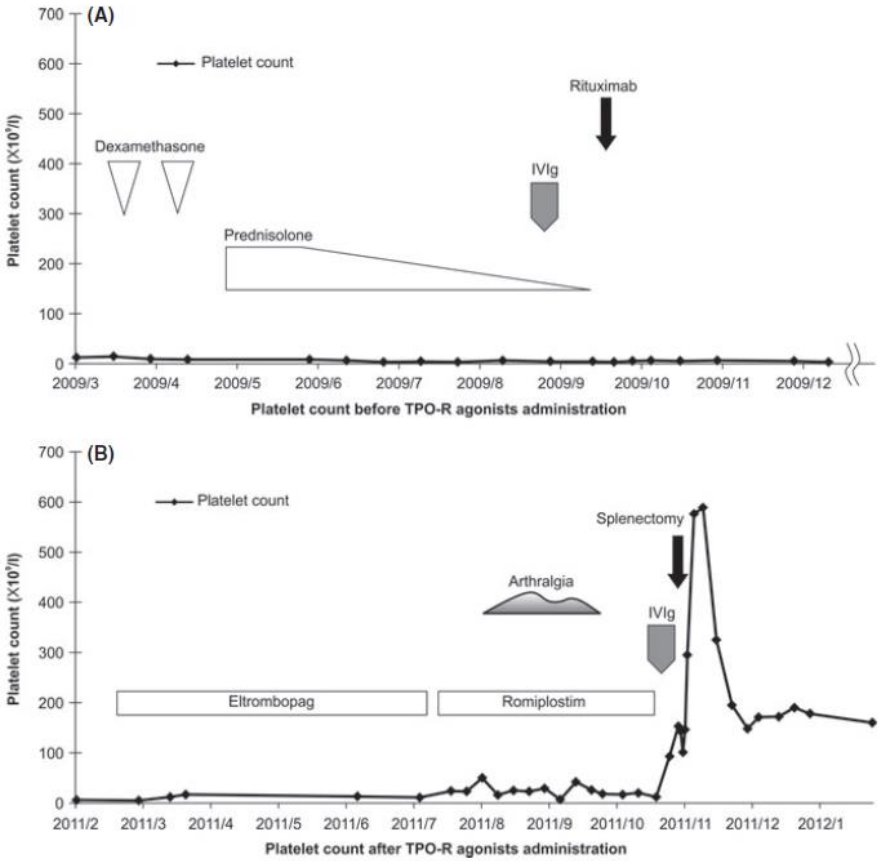



Change in platelet counts according to treatment phases. Dosage of steroids, immunoglobulins and romiplostim are detailed in the text. Plt Tx, platelet transfusions.

***Sivera et al, BCF 2012***

# Combined romiplostim and intravenous immunoglobulin therapy increased platelet count, facilitating splenectomy in a patient with refractory immune thrombocytopenic purpura unresponsive to monotherapy

***Mitsuhashi et al, 2012***



JGH Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/j.1440-1746.2012.07246.x

HEPATOLOGY

# Preoperative use of romiplostim in thrombocytopenic patients with chronic hepatitis C and liver cirrhosis

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*Internal Medicine and Hematology Department, and †Clinical Pathology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

2013

**Table 1** Patient demographics, baseline characteristics and laboratory assessments at baseline and end-of-study

| Characteristic | | Mean |
|---|---|---|
| Male sex, *n* (%) | | 35 (100) |
| Mean age, years (range) | | 46.2 (37–58) |
| Baseline platelet count, $\times 10^9$/L (SD) | | 31 (6) |
| Peak platelet count, $\times 10^9$/L (SD) | | 86 (11) |
| | Baseline | 90 days |
| Alanine aminotransferase, IU/L (SD) | 42.6 (13.5) | 42.5 (12.7) |
| Aspartate aminotransferase, IU/L (SD) | 42.5 (13.5) | 46.1 (15.2) |
| Total bilirubin, mg/dL (SD) | 1.66 (0.64) | 1.67 (0.63) |
| Direct bilirubin, mg/dL (SD) | 0.96 (0.40) | 0.96 (0.40) |
| Albumin, g/dL (SD) | 3.53 (0.45) | 3.54 (0.39) |
| International normalized ratio (SD) | 1.49 (0.24) | 1.47 (0.21) |
| Total leukocyte count, $\times 10^9$/L (SD) | 4.08 (1.18) | 4.22 (1.29) |
| Hemoglobin, g/dL (SD) | 11.27 (1.09) | 11.33 (1.01) |

SD, standard deviation.

**Table 2** Perioperative characteristics for each patient enrolled in the study

| Patient | Age (years) | Surgical procedure | Baseline Child–Pugh parameters | | | | | | Platelet count ($\times 10^9$/L) | | Time from initial romiplostim treatment to surgery (days) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total bilirubin mg/dL | Albumin g/dL | INR | Hepatic encephalopathy grade | Ascites | Child–Pugh score | Baseline | Surgery | |
| 1 | 50 | Cataract | 3.1 | 2.8 | 2.2 | 2 | Severe | 12 | 25 | 92 | 27 |
| 2 | 42 | Hernia | 2.2 | 3.5 | 1.8 | 4 | Severe | 12 | 30 | 105 | 30 |
| 3 | 44 | Hip replacement | 1.2 | 4.1 | 1.4 | 4 | Severe | 11 | 41 | 225 | 24 |
| 4 | 58 | Cataract | 2.5 | 3.2 | 1.7 | 3 | Severe | 12 | 22 | 82 | 30 |
| 5 | 45 | Hernia | 1.4 | 3.6 | 1.6 | 3 | Severe | 10 | 35 | 88 | 33 |
| 6 | 51 | Cataract | 2.4 | 3.8 | 1.56 | 3 | Severe | 10 | 46 | 191 | 24 |
| 7 | 46 | Hernia | 2 | 4.2 | 1.3 | 3 | Severe | 10 | 21 | 98 | 39 |
| 8 | 53 | Fracture fixation | 2 | 4.7 | 1.4 | 3 | Severe | 10 | 33 | 150 | 27 |
| 9 | 49 | Fracture fixation | 2.6 | 3.1 | 1.7 | 3 | Severe | 12 | 23 | N/A† | N/A† |
| 10 | 50 | Cataract | 1.1 | 3.8 | 1.7 | 3 | Severe | 10 | 21 | 85 | 30 |
| 11 | 47 | Fracture fixation | 1.7 | 4 | 1.7 | 3 | Severe | 10 | 42 | 222 | 21 |
| 12 | 43 | Hernia | 2.3 | 3.3 | 1.8 | 2 | Severe | 11 | 36 | 92 | 24 |
| 13 | 45 | Hip replacement | 1 | 3.5 | 1.3 | 3 | Severe | 10 | 35 | 240 | 21 |
| 14 | 41 | Fracture fixation | 0.9 | 3.3 | 1.2 | 3 | Severe | 10 | 28 | 90 | 30 |
| 15 | 39 | Cataract | 2 | 2.9 | 1.5 | 3 | Severe | 11 | 32 | 152 | 30 |
| 16 | 50 | Hernia | 1.6 | 3.9 | 1.7 | 3 | Severe | 10 | 43 | 96 | 18 |
| 17 | 53 | Hip replacement | 2.1 | 3.2 | 1.4 | 3 | Severe | 11 | 37 | 75 | 21 |
| 18 | 44 | Hernia | 2 | 4.1 | 1.3 | 3 | Severe | 10 | 42 | 206 | 21 |
| 19 | 48 | Cataract | 3.1 | 2.8 | 1.8 | 2 | Severe | 13 | 31 | 84 | 27 |
| 20 | 42 | Hernia | 1.1 | 3.5 | 1.7 | 3 | Severe | 10 | 26 | 93 | 27 |
| 21 | 39 | Fracture fixation | 1.8 | 3.2 | 1.5 | 3 | Severe | 10 | 30 | 146 | 33 |
| 22 | 42 | Hip replacement | 0.8 | 3.5 | 1.4 | 3 | Severe | 10 | 26 | 82 | 30 |
| 23 | 51 | Cataract | 1.1 | 3.5 | 1.2 | 3 | Severe | 10 | 28 | 91 | 18 |
| 24 | 48 | Fracture fixation | 2.1 | 3.3 | 1.4 | 3 | Severe | 11 | 32 | 156 | 21 |
| 25 | 47 | Hernia | 1 | 3.5 | 1.3 | 3 | Severe | 10 | 29 | 82 | 27 |
| 26 | 53 | Hernia | 0.9 | 3.5 | 1.7 | 3 | Severe | 11 | 31 | 94 | 21 |
| 27 | 46 | Cataract | 1.3 | 3.3 | 1.5 | 3 | Severe | 10 | 34 | 164 | 21 |
| 28 | 41 | Hip replacement | 1.6 | 3.2 | 1.4 | 3 | Severe | 10 | 29 | 82 | 21 |
| 29 | 37 | Hernia | 0.9 | 3.5 | 1.7 | 3 | Severe | 11 | 27 | 91 | 21 |
| 30 | 50 | Fracture fixation | 1.4 | 3.8 | 1.8 | 3 | Severe | 10 | 33 | 102 | 21 |
| 31 | 44 | Cataract | 1.9 | 3.1 | 1.6 | 3 | Severe | 10 | 29 | 86 | 24 |
| 32 | 39 | Cataract | 1 | 3.2 | 1.5 | 3 | Severe | 10 | 34 | 104 | 24 |
| 33 | 51 | Fracture fixation | 1.8 | 3.2 | 1.6 | 3 | Severe | 10 | 27 | 90 | 27 |
| 34 | 48 | Hernia | 1.1 | 3.3 | 1.7 | 3 | Severe | 10 | 31 | 97 | 18 |
| 35 | 41 | Cataract | 2.2 | 2.9 | 1.9 | 3 | Severe | 11 | 25 | N/A† | N/A† |

†N/A, not applicable; these non-responders did not undergo surgery.
INR, international normalized ratio.

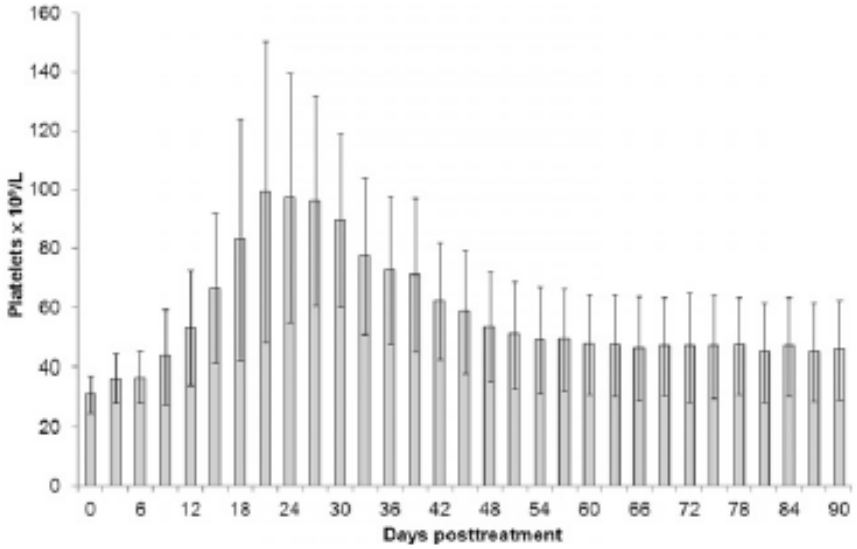


**Figure 1** Mean platelet count during the 3-month study period. The mean platelet count ± standard deviation (SD) for the 35 patients determined every third day is shown. The mean platelet count increased to a transient maximum of 99 ± 36 × $10^9$/L after 21 days.

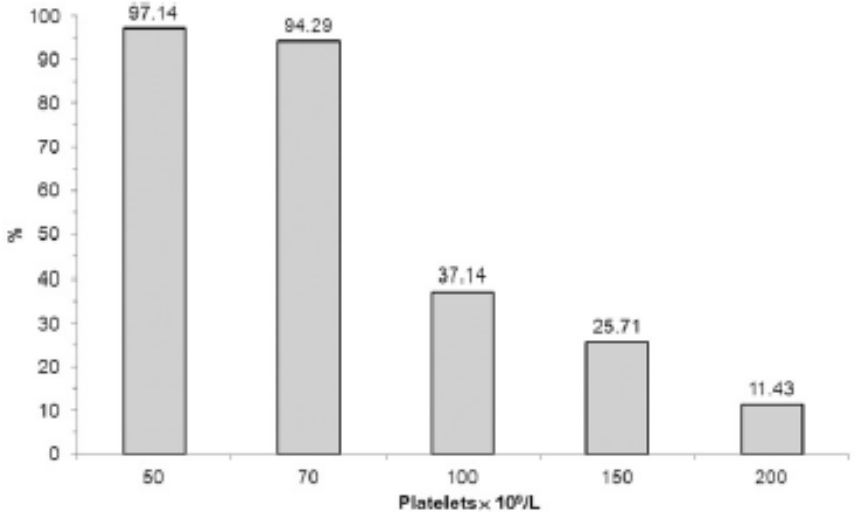


**Figure 2** Peak platelet count. The percentage of patients reaching peak platelet counts of ≥ 50, 70, 100, 150 and 200 × $10^9$/L (day 18 to 39).

No serious adverse events were observed during the romiplostim treatment period (up to day 30). Following surgical interventions, none of the subjects experienced postoperative bleeding episodes, and none experienced a thrombotic event within 60 postoperative days.

INTERNAL MEDICINE JOURNAL

# Use of romiplostim in patients with chronic idiopathic thrombocytopenic purpura during perioperative period

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[1]Southern Haematology and Cancer Research Institute and [2]Graduate School of Medicine, University of Wollongong, Wollongong, New South Wales, Australia

*2015*

Romiplostim 3µg/kg subcutaneously on day 15 pre-operatively.

↓

Repeat FBC on day 10-12 pre-operatively. Platelet count(x$10^9$/L):

↙ ↘

If count <100, increase romiplostim dosage by 1µg/kg and administer on day 7 pre-op.

If count >100, repeat romiplostim dosage (3µg/kg) on day 7 pre-op.

↓ ↓

Repeat FBC Day 3 pre-op and if platelet count <100, repeat romiplostim dosage.

↓

Repeat FBC day 0.

↙ ↘

If platelet count >80 x$10^9$/L.

If platelet count <80 x$10^9$/L.

↓ ↓

Surgery day 0

Discuss with surgeon and determine appropriate treatment plan.

↓

Repeat FBC day 7 post-op. If platelet count <50, repeat romiplostim administration.

↓

Repeat FBC 4 weeks post-op to ensure platelet count returns to base line or better, no rebound thrombocytopenia.

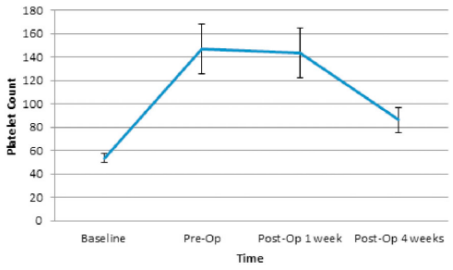


**Figure 2** Patients' mean platelet counts during romiplostim treatment. Platelet counts were taken at baseline, preoperatively (Pre-Op), 1 week postoperative (Post-Op 1 week) and 4 weeks postoperative (Post-Op 4 weeks).

**Table 1** Summary of patient characteristics, results of platelet counts and complications

| Patient no. | Gender | Age | Type of surgery | Baseline platelets | Preoperative platelets | One-week postoperative platelets | One-month postoperative platelets | Platelet function | Cardiolipin antibodies | Lupus inhibitor | Complications |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 63 | Mitral valve replacement | 65 | 139 | 174 | 146 | Abnormal | Positive, IgG 16, beta 2 glycoprotein <20 | Not detected | Nil |
| 2 | M | 65 | Mitral valve replacement | 35 | 100 | 70 | 40 | Abnormal | Negative | Not detected | Nil |
| 3 | M | 52 | Liver biopsy | 32 | 114 | 80 | 45 | Abnormal | Cardiolipin IgG 14/IgM 9/beta2 glycoprotein IgG <20 | Not detected | Headache |
| 4 | M | 52 | Thyroidectomy | 35 | 145 | 164 | 97 | Abnormal | Negative | Not detected | Nil |
| 5 | M | 52 | Aortic valve replacement | 68 | 215 | 128 | 166 | Abnormal | Negative | Not detected | Nil |
| 6 | F | 46 | Mucosectomy | 39 | 122 | 139 | 86 | Normal | Negative | Not detected | Nil |
| 7 | M | 69 | Coronary artery bypass graft | 51 | 104 | 52 | 57 | N/A | Negative | Not detected | Nil |
| 8 | M | 56 | Cystoscopy and prostate enucleation | 75 | 207 | 200 | 114 | Abnormal | Negative | Not detected | Nil |
| 9 | M | 45 | Thyroidectomy and neck dissection | 64 | 420 | 42 | 62 | Normal | Positive, IgG 20, beta 2 glycoprotein <20 | Not detected | Rebound thrombocytopenia |
| 10 | M | 75 | Spinal surgery | 62 | 104 | 247 | 73 | Abnormal | Negative | Not detected | Nil |
| 11 | F | 59 | Colonoscopy/gastroscopy | 54 | 50 | 134 | 51 | N/A | Negative | Not detected | Had a delayed response to therapy |
| 12 | F | 58 | Liver biopsy | 47 | 104 | 102 | 89 | N/A | Negative | Not detected | Nil |
| 13 | M | 64 | Colon polypectomy | 39 | 70 | 40 | 36 | Abnormal | Positive, IgG 16, beta 2 glycoprotein <20 | Not detected | Platelet count only 70 preoperative. Surgeon happy to go ahead |
| 14 | M | 57 | Cholecystectomy | 75 | 255 | 403 | 57 | N/A | Negative | Not detected | Delayed rebound thrombocytopenia |
| 15 | M | 18 | Tonsillectomy | 46 | 107 | 151 | 190 | N/A | Negative | Not detected | Nil |
| 16 | F | 43 | Cholecystectomy | 61 | 106 | 159 | 81 | Normal | Negative | Not detected | Nil |
| 17 | M | 84 | Hernia repair | 67 | 144 | 157 | 80 | N/A | Negative | Not detected | Nil |
| 18 | M | 62 | Tooth extraction | 65 | 127 | 99 | 64 | Abnormal | Negative | Not detected | Nil |
| 19 | M | 78 | Coronary artery bypass graft | 73 | 119 | 76 | 76 | Normal | Negative | Not detected | Nil |
| 20 | F | 47 | Cholecystectomy | 74 | 106 | 159 | 109 | Normal | Negative | Not detected | Nil |
| 21 | M | 77 | Invasive eye surgery | 70 | 127 | 113 | 73 | Normal | Negative | Not detected | Nil |
| 22 | F | 58 | Colon polypectomy | 37 | 98 | 43 | 41 | Abnormal | Negative | Not detected | Nil |
| Average | | 58.2 | | 56.1 | 140.1 | 133.3 | 83.3 | | | | |
| SD | | 14.4 | | 15.0 | 77.9 | 81.5 | 40.8 | | | | |
| Range | | 18–84 | | 32–75 | 50–420 | 40–403 | 36–190 | | | | |
| Standard error | | 3.1 | | 3.2 | 16.4 | 17.4 | 8.7 | | | | |

All patients responded to therapy and only two patients required additional third romiplostim therapy.

In 10 of 22 patients (45%, 95% CI 24–66%) a platelet count response ≥80 × 109/L was maintained at 1 month following surgery, hence a sustained response.

However, two patients achieved a <50% increase from baseline in their platelet count, but did not experience any postoperative complications.

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informa
healthcare

ORIGINAL ARTICLE

# Hemostatic challenges in patients with chronic immune thrombocytopenia treated with eltrombopag

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[1]*Department of Pediatric Hematology/Oncology, University of Illinois College of Medicine-Peoria, Peoria, IL, USA and* [2]*GlaxoSmithKline, Collegeville, PA, USA*

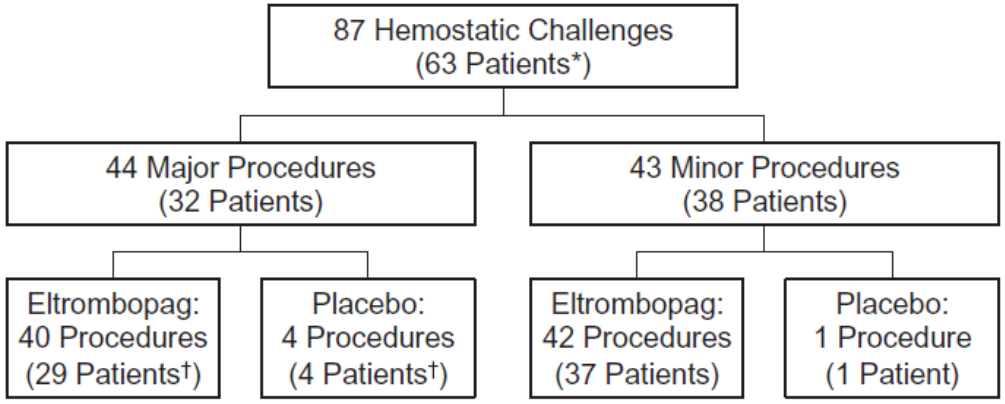



Figure 1. Hemostatic challenges and bleeding events across the eltrombopag ITP clinical program.
*The total of 63 patients includes 7 patients who had both major and minor procedures.
†One patient with a hemostatic challenge received placebo in Study 773B and subsequently received open-label eltrombopag in the EXTEND study; this patient underwent a major procedure in each study.

In this analysis of data from five studies of eltrombopag in patients with chronic ITP, patients treated with eltrombopag had median platelet counts of 100 000/ml before major invasive procedures and 82 000/ml before minor procedures.

These findings are in line with recent clinical guidelines for the identification and management of ITP [2], which recommend a target platelet count of at least 80 000/ml before a major procedure and at least 50 000/ml before a minor procedure.

None of the patients who had received placebo and underwent a hemostatic challenge had platelet levels above these targets prior to the procedures. Although none of the 4 patients in the placebo group who underwent a major procedure had a bleeding event recorded, 2 of them required supplemental ITP treatment.

Table I. Major hemostatic challenges during (or within 10 days after) study treatment.

| Study Sex/Age | Treatment | Major hemostatic challenge | | Platelet count (/μl) | | | | Supplemental ITP treatment | | Bleeding event[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Before | | After | | | | |
| | | Day | Procedure | Day | Count | Day | Count | Day | Treatment | |
| **773A** | | | | | | | | | | |
| F/53 | 50 mg | 24 | Cholecystectomy | 15 | 428 000 | 29 | 114 000 | | | |
| F/53 | 50 mg | 29 | Laparoscopic cholecystectomy | 22 | 369 000 | 36 | 319 000 | | | |
| F/57[e1] | 75 mg | 9 | Motor vehicle accident | 8 | 491 000 | 57 | 4000 | | | |
| F/36 | Placebo | 19[b] | Trabeculectomy | 12 | 12 000 | 36 | 26 000 | 12, 13 | IVIg | |
| **773B** | | | | | | | | | | |
| M/69 | Placebo | 29 | Hip arthroplasty | 22 | 25 000 | 71 | 86 000 | 22, 23 | IVIg | |
| | | | | | | | | 29 | Transfusion | |
| F/27[e2,f1] | Placebo | 37 | Excision papilloma | 36 | 36 000 | 43 | 32 000 | | | |
| **RAISE** | | | | | | | | | | |
| M/62[f2] | 50 mg | 93 | Aortic aneurysm repair | 71 | 123 000 | 98 | 292 000 | 93 | Transfusion | |
| F/67[f3] | 50 mg | 119 | Tendon sheath incision | 112 | 117 000 | 140 | 109 000 | | | |
| F/51[f4] | 50 mg | 107 | Hysterectomy | 105 | 175 000 | 132 | 280 000 | | | |
| F/59[e3] | 50 mg | 95[c] | Colectomy | 85 | 2000 | 211 | 1000 | 92 | IVIg | Yes |
| | | 97[c] | Laparotomy | 85 | 2000 | 211 | 1000 | | | |
| F/18 | Placebo | 91 | Limb operation | 85 | 6000 | 101 | 9000 | | | |
| **REPEAT** | | | | | | | | | | |
| F/56[e4] | 50 mg | 48 | Sinus operation | 43 | 83 000 | 50 | 359 000 | | | Yes |
| M/63 | 50 mg | 84 | Transurethral prostatectomy | 83 | 126 000 | 92 | 261 000 | | | |
| M/71 | 50 mg | 162[d] | Biopsy pancreas | 157 | 128 000 | 164 | 77 000 | | | |
| M/48 | 50 mg | 64 | Colon polypectomy | 61 | 130 000 | 68 | 123 000 | | | |
| **EXTEND** | | | | | | | | | | |
| F/28[f1] | 50 mg | 258 | Biopsy cervix | 228 | 27 000 | 263 | 39 000 | | | |
| M/63[f2] | 50 mg | 93 | Hip arthroplasty | 90 | 75 000 | 118 | 357 000 | 93 | Platelet transfusion | |
| F/68[f3] | 50 mg | 141M | Cystocele repair | 135 | 412 000 | 148 | 54 000 | | | |
| | | 141 | Cystopexy | | | | | | | |
| | | 141 | Enterocele | | | | | | | |
| | | 141 | Vaginal vault prolapse repair | | | | | | | |
| F/75[f4] | 50 mg | 351 | Carpal tunnel decompression | 337 | 92 000 | 365 | 63 000 | | | |
| | | 351 | Tendon sheath incision | | | | | | | |
| F/59 | 50 mg | 205 | Hip arthroplasty | 190 | 62 000 | 239 | 116 000 | 141[g] | Mycophenolic acid | |
| | | | | | | | | 198, 199 | IVIg | |
| M/30[e5] | 50 mg | 474 | Splenectomy | 448 | 0 | 484 | 43 000 | 465–473 | Prednisolone | |
| M/71 | 50 mg | 511 | Hip arthroplasty | 508 | 79 000 | 536 | 265 000 | | | |
| | | 518 | Catheterisation cardiac | 508 | 79 000 | 536 | 265 000 | | | |
| M/55 | 50 mg | 449 | Incisional drainage | 442 | 85 000 | 467 | 106 000 | | | |
| F/49 | 50 mg | 204 | Cataract operation right[h] | 184 | 152 000 | 215 | 96 000 | | | |
| | | 425 | Cataract operation left[h] | 418 | 140 000 | 448 | 165 000 | | | |
| F/50[e6] | 50 mg | 353 | Micrographic skin surgery | 349 | 88 000 | 358 | 94 000 | | | |
| F/54 | 50 mg | 312 | Splenectomy | 308 | 90 000 | 332 | 44 000 | | | |
| F/52[e7] | 50 mg | 150 | Medical device implantation | 87 | 19 000 | – | – | | | |

Table 1. Continued.

| Study Sex/Age | Treatment | Major hemostatic challenge | | Platelet count (/μl) | | | | Supplemental ITP treatment | | Bleeding event[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Before | | After | | | | |
| | | Day | Procedure | Day | Count | Day | Count | Day | Treatment | |
| F/65 | 50 mg | 293 | Ovarian operation | 286 | 108 000 | 309 | 208 000 | | | |
| F/68 | 50 mg | 176 | Cataract operation[i] | 175 | 88 000 | 182 | 48 000 | | | |
| | | 204 | Cataract operation[i] | 189 | 74 000 | 210 | 54 000 | | | |
| F/65 | 50 mg | 71 | Cataract operation[h] | 56 | 16 000 | 78 | 158 000 | | | |
| F/38 | 50 mg | 172 | Uterine polypectomy | 155 | 117 000 | 183 | 174 000 | | | |
| F/76 | 50 mg | 548 | Femur fracture | 540 | 89 000 | 575 | 76 000 | | | |
| F/75 | 50 mg | 216 | Carpal tunnel decompression | 210 | 205 000 | 224 | 76 000 | | | |
| M/42 | 50 mg | 123 | Arthroscopy | 122 | 42 000 | 150 | 35 000 | | | |
| F/57 | 50 mg | 98 | Splenectomy | 98 | 256 000 | 99 | 328 000 | | | |
| F/46 | 50 mg | 468 | Hemorrhoid operation | 460 | 264 000 | 467 | 38 000 | | | |

[a]See text for details of reported bleeding adverse events.

Patients were still on study at the time of the hemostatic challenge, except as follows: [b]study medication had stopped on day 12 to switch patient to IVIg prior to operation; [c]study medication had stopped on day 91 due to adverse event; [d]study medication had stopped on day 157 for unspecified reason.

[e]Seven patients (labeled e1 to e7 in this table and in Table II) underwent a major procedure and a minor procedure.

[f]Four patients (labeled f1 to f4) underwent a major procedure in both a parent study and in the EXTEND study.

[g]Supplemental ITP treatment was ongoing at the time of study completion on day 253.

[h]Cataracts were present at baseline in this patient and were not considered related to eltrombopag treatment.

[i]Cataracts were present at baseline in this patient and worsening of cataracts was considered related to eltrombopag treatment.

Table II. Minor hemostatic challenges during (or within 10 days after) study treatment.

| Study Sex/Age | Treatment | Minor hemostatic challenge | | Platelet count (/μl) | | | | Supplemental ITP treatment | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | After | | Before | | | |
| | | Day | Procedure | Day | Count | Day | Count | Day | Treatment |
| **RAISE** | | | | | | | | | |
| F/59[e1] | 50 mg | 87 | Colonoscopy | 85 | 2000 | 211 | 1000 | | |
| F/80 | 50 mg | 10 | Skin lesion | 8 | 49 000 | 17 | 163 000 | 1–11 | Prednisone |
| F/47 | 50 mg | 16[a] | Lumbar puncture | 16 | 339 000 | 21 | 375 000 | 83–91 | Methylprednisolone |
| F/48 | 50 mg | 82 | Lumbar puncture | 78 | 79 000 | 96 | 17 000 | 86 | Anti-D Ig |
| | | | | | | | | 87 | Transfusion |
| M/52 | 50 mg | 54[b] | Endoscopy (GI) | 50 | 34 000 | 105 | 31 000 | | |
| | | 93[b] | Endoscopy (GI) | 50 | 34 000 | 105 | 31 000 | | |
| F/47 | 50 mg | 166 | Biopsy | 160 | 342 000 | 168 | 365 000 | | |
| | | 166 | Skin operation | | | | | | |
| F/72 | 50 mg | 114 | Skin biopsy | 111 | 180 000 | 118 | 190 000 | | |
| F/33 | Placebo | 141 | Bone marrow biopsy | 141 | 20 000 | 155 | 21 000 | | |
| **REPEAT** | | | | | | | | | |
| F/56 | 50 mg | 41 | Colonoscopy | 36 | 101 000 | 43 | 112 000 | | |
| F/59 | 50 mg | 111 | Endoscopy (upper GI) | 106 | 528 000 | 113 | 280 000 | | |
| F/53 | 50 mg | 113 | Colonoscopy | 106 | 107 000 | 114 | 85 000 | | |
| **EXTEND** | | | | | | | | | |
| F/58[e2] | 50 mg | 210 | Bronchoscopy | 209 | 227 000 | 215 | 44 000 | 250–251 | IVIg |
| | | 252 | Bone marrow biopsy | 252 | 29 000 | 256 | 20 000 | | |
| F/49[e3] | 50 mg | 396 | Bone marrow biopsy | 396 | 46 000 | 425 | 56 000 | | |
| F/57[e4] | 50 mg | 334 | Colonoscopy | 329 | 139 000 | 369 | 168 000 | | |
| M/30[e5] | 50 mg | 386 | Bone marrow biopsy | 386 | 0 | 420 | 0 | 463 | IVIg |
| | | 462 | Lumbar puncture | 448 | 0 | 484 | 43 000 | | |
| F/50[e6] | 50 mg | 211 | Skin biopsy | 202 | 80 000 | 230 | 87 000 | | |
| F/52[e7] | 50 mg | 130 | Dialysis | 87 | 19 000 | — | — | | |
| F/56 | 50 mg | 102 | Endoscopy | 101 | 3000 | 113 | 975 000 | 96, 101–105 | IVIg |
| | | | | | | | | 101–104 | Dexamethasone |
| M/54 | 50 mg | 56 | Colonoscopy | 56 | 87 000 | 62 | 102 000 | | |
| F/70 | 50 mg | 353 | Endoscopy (upper GI) | 337 | 209 000 | 365 | 189 000 | | |
| F/82 | 50 mg | 471 | Colonoscopy | 461 | 36 000 | 489 | 140 000 | | |
| F/61 | 50 mg | 15 | Colonoscopy | 8 | 204 000 | 17 | 510 000 | | |
| F/80 | 50 mg | 29 | Skin neoplasm excision | 29 | 268 000 | 34 | 208 000 | | |
| M/78 | 50 mg | 389[c] | Endoscopy | 387 | 248 000 | 400 | 185 000 | | |
| F/49 | 50 mg | 42 | Bone marrow biopsy | 42 | 28 000 | 48 | 26 000 | | |
| F/65 | 50 mg | 131 | Colonoscopy | 127 | 96 000 | 134 | 265 000 | | |
| M/68 | 50 mg | 313 | Acrochordon excision | 288 | 56 000 | 316 | 68 000 | | |
| F/22 | 50 mg | 348 | Endoscopy (upper GI) | 344 | 156 000 | 351 | 76 000 | | |
| F/45 | 50 mg | 83[d] | Stem cell transplant | 82 | 41 000 | 89 | 29 000 | 74–79 | Transfusion |
| | | | | | | | | 75–97 | Prednisolone |
| | | | | | | | | 80 | Anti-D Ig |
| F/45 | 50 mg | 656 | Tissue sealing | 649 | 54 000 | 670 | 164 000 | | |
| F/55 | 50 mg | 100 | Endoscopy (upper GI) | 100 | 100 000 | 108 | 29 000 | | |
| F/51 | 50 mg | 414 | Bone marrow biopsy | 414 | 88 000 | 443 | 77 000 | | |
| F/68 | 50 mg | 406 | Bone marrow biopsy | 406 | 5000 | 416 | 2000 | | |
| F/47 | 50 mg | 31 | Bone marrow biopsy | 31 | 77 000 | 37 | 61 000 | 32–60 | Prednisolone |
| F/53 | 50 mg | 19 | Suture insertion | 19 | 450 000 | 31 | 6000 | | |
| F/57 | 50 mg | 227 | Tumor excision | 225 | 64 000 | 232 | 73 000 | 221–224 | Methylprednisolone |
| F/60 | 50 mg | 402 | Bone marrow biopsy | 388 | 159 000 | 409 | 123 000 | | |
| F/43 | 50 mg | 85 | Colonoscopy | 82 | 82 000 | 92 | 74 000 | | |
| | | 85 | Endoscopy (upper GI) | | | | | | |

No bleeding adverse events were reported after minor hemostatic challenges.

Patients were still on study at the time of the hemostatic challenge, except as follows: [a]study medication was stopped on day 15 due to adverse event; [b]study medication was stopped on day 53 due to adverse event; [c]study medication was stopped on day 387 due to adverse event; [d]study medication was stopped on day 75 due to lack of efficacy.

[e]Seven patients (labeled e1 to e7 in this table and in Table I) underwent a major procedure and a minor procedure.

RESEARCH ARTICLE

AJH

2016

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

Francesco Zaja,[1]* Wilma Barcellini,[2] Silvia Cantoni,[3] Monica Carpenedo,[4] Giuseppe Caparrotti,[5] Valentina Carrai,[6] Nicola Di Renzo,[7] Cristina Santoro,[8] Massimo Di Nicola,[9] Dino Veneri,[10] Federico Simonetti,[11] Anna M. Liberati,[12] Valeria Ferla,[2] Francesca Paoloni,[13] Enrico Crea,[13] Stefano Volpetti,[1] Enrica Tuniz,[1] and Renato Fanin[1]

| | |
|---|---|
| **Patients** | **31**<br>**median age 50 yrs, range 19-81** |
| **Previous treatments** | **One or two lines n=12**<br>**Three or more lines n=19** |
| **Planned surgery** | **Splenectomy n= 31** |

| | |
|---|---|
| **Platelet count (median)** | **11,000/mmc** |
| **TPO-receptor agonists** | **RPL / ETP 24 /7** |
| **Concomitant medication** | **n= 19 (61.3%)** |
| **Months after starting TPO-RA (median)** | **86.5 days** |
| **Platelet count at surgery** | **Response in 24 patients (77.4%) (median platelet count at splenectomy 114,000/mmc, without difference in the TPO-RA effect)** |
| **Refusal of splenectomy** | **n= 2** |
| **Postoperative bleeding** | **n= 1 (grade 4), platelet count 30,000/mmc** |
| **Thrombosis post-splenectomy** | **n= 2 (Plts 260 and 178,000/mmc) (6.8%), in one case without LMWH** |

***PREOPERATIVE USE OF THROMBOPOIETIN RECEPTOR AGONISTS IN ITP PATIENTS PRIOR TO SPLENECTOMY OR OTHER SURGICAL PROCEDURES.***

**E. Rossi et al, EHA 2014 With added contribution of: S. Cantoni, M. Carpenedo, U. Consoli**

| Case | Sex | Age | TPO-RA | Duration of treatment (months) | Maximum dosage | Concomitant steroids (<1 mg/kg/d) | Response ≥30x10$^9$/L | Rescue treatment | PC at surgery x 10$^9$/L |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 16 | RPL | 6,0 | 8 µgr/kg/wk | yes | yes | N/A | ¶ |
| 2 | F | 48 | RPL | 7,9 | 3 µgr/kg/wk | yes | yes | N/A | 110 |
| 3 | M | 34 | RPL | 2,2 | 8 µgr/kg/wk | no | yes | N/A | 75 |
| 4 | F | 24 | RPL | 8,4 | 8 µgr/kg/wk | yes | yes | N/A | 180 |
| 5 | M | 33 | RPL | 12,6 | 10 µgr/kg/wk | no | no | ELT 350 mg/wk | 49 |
| 6 | F | 71 | RPL | 50,5 | 2 µgr/kg/wk | yes | yes | N/A | 102 |
| 7 | M | 68 | RPL | 7,2 | 3 µgr/kg/wk | no | yes | N/A | 151 |
| 8 | F | 58 | RPL | 7,6 | 6 µgr/kg/wk | no | yes | N/A | 35 |
| 9 | F | 50 | RPL | 3,1 | 9 µgr/kg/wk | no | no | HD-S | 152 |
| 10 | F | 24 | RPL | 1,2 | 7 µgr/kg/wk | no | no | HD-S / HD- IG | 436 |
| 11 | M | 32 | RPL | 1,1 | 4 µgr/kg/wk | yes | no | PLT. TR. | 45 |
| 12 | M | 64 | RPL | 1,8 | 3 µgr/kg/wk | no | yes | N/A | 302 |
| 13 | F | 22 | RPL | 1,8 | 10 µgr/kg/wk | no | yes | N/A | 321 |
| 14 | F | 20 | RPL | 18,6 | 3 µgr/kg/wk | no | yes | N/A | 40 |
| 15 | M | 58 | ETP | 1,9 | 525 mg/wk | yes | yes | N/A | 178 |
| 16 | M | 32 | ETP | 7,3 | 100 mg/wk | no | yes | N/A | 194 |
| 17 | F | 65 | ETP | 1,9 | 525 mg/wk | yes | yes | N/A | 254 |
| 18 | F | 47 | ETP | 3,7 | 350 mg/wk | no | yes | N/A | 96 |
| 19 | F | 57 | ETP | 24,1 | 525 mg/wk | no | no | RPL 10 µgr/kg/wk | 207 |
| 20 | M | 17 | ETP | 4,1 | 525 mg/wk | yes | no | RPL 10 µgr/kg/wk and then HD-IG | 721 |
| 21 | M | 19 | ETP | 12 | 525 mg/wk | yes | no | HD-IG | 101 |
| 22 | F | 19 | ETP | 23,8 | 350 mg/wk | no | yes | N/A | 128 |
| 23 | M | 19 | ETP | 4,3 | 350 mg/wk | no | yes | N/A | 171 |
| 24 | F | 43 | ETP | 10,0 | 525 mg/wk | no | no | HD-S | 40 |
| 25 | M | 47 | ETP | 13,5 | 525 mg/wk | no | yes | N/A | 250 |

| Case | Sex | Age | Previous splenectomy | Basal PC x $10^9$/L | TPO-RA | Duration of treatment (months) | Maximum dosage | Concomitant steroids (<1 mg/kg/d) | Response ≥30x$10^9$/L | Procedure | PC at surgery x $10^9$/L |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 26 | M | 75 | no | 17 | RPL | 4,8 | 4µgr/kg/wk | yes | yes | aortic valve replacement | 238 |
| 27 | M | 60 | no | 6 | RPL | 1,3 | 5 µgr/kg/wk | no | yes | carotid endarterectomy | 398 |
| 28 | F | 44 | no | 29 | RPL | 2,9 | 4 µgr/kg/wk | yes | yes | hysteroscopic polypectomy | 150 |
| 29 | M | 63 | no | 48 | RPL | 1,1 | 4 µgr/kg/wk | no | yes | brain neurosurgery | 103 |
| 30 | F | 43 | yes | 30 | ETP | 1,9 | 175 mg/wk | no | yes | mastectomy | 207 |
| 30 | F | 45 | yes | 15 | ETP | 0,5 | 175 mg/wk | no | yes | breast implant | 139 |
| 31 | M | 71 | no | 23 | ETP | 3,4 | 350 mg/wk | no | yes | total hip replacement | 144 |
| 32 | F | 20 | no | 3 | ETP | 0,6 | 350 mg/wk | no | yes | thyroglossal cyst removal | 101 |
| 33 | F | 24 | no | 42 | ETP | 2,4 | 525 mg/wk | no | yes | lymph node biopsy | 34 |
| 34 | F | 23 | no | 41 | ETP | 0,6 | 275 mg/wk | no | yes | tonsillectomy | 473 |
| 35 | F | 65 | yes | 9 | ETP | 1,2 | 225 mg/wk | yes | yes | lung lobectomy | 51 |
| 36 | F | 66 | no | 30 | ETP | 1,1 | 150 mg/wk | no | yes | aortic, mitral, and tricuspid valve replacement | 143 |
| 37 | M | 64 | no | 42 | ETP | 2,5 | 350 mg/wk | no | yes | hemorrhoidectomy | 65 |

| | Romiplostim | Eltrombopag | P |
|---|---|---|---|
| **Male sex, %** | 8/17, 47% | 8/19, 42% | 1.00 |
| **Age, median (range)** | 48 (20-75) | 45 (17-71) | 0.56 |
| **Previous lines of therapy, median (range) ¶** | 2 (1-4) | 2 (0-7) | 0.80 |
| **Previous splenectomy, %** | 0/18, 0% | 2/19, 10% | 0.48 |
| **Basal platelet count x $10^9$/L (median, range)** | 9 (2-48) | 18 (3-42) | 0.29 |
| **Duration of treatment, months (median, range)** | 3.1 (1.1-50.5) | 3.4 (1.1-24.1) | 0.69 |
| **Concomitant steroids (< 1 mg/kg/d), %** | 6/17, 35% | 5/19, 26% | 0.72 |
| **Splenectomy vs other procedures, %** | 13/17, 76% | 11/19, 58% | 0.30 |
| **Complete response (> 100 x $10^9$/L), %** | 13/19, 68% | 11/20, 55% | 0.51 |
| **Response (> 30 x $10^9$/L), %** | 15/20, 75% | 16/20, 80% | 1.00 |
| **Platelet count at surgery x $10^9$/L (median, range)** | 150 (40-436) | 143 (34-721) | 0.98 |
| **Platelet count at d + 14 x $10^9$/L (median, range)** | 204 (49-751) | 462 (82-840) | 0.13 |

No major bleeding complication was recorded in any patient.

Two clinically relevant non-major bleeding in 2 patients (tonsillectomy and hemorrhoidectomy)

One pulmonary embolism (RPL, no LMWH) after splenectomy

One portal vein thrombosis (HD-Ig, LMWH) after splenectomy

Pooling the present series with the cases of Zaja et al (AJH 2016) the rate of VTE after splenectomy was 9.1% (4 of 44); the rate of VTE (other than PVT) after TPO-RAs was 2 of 38 (5.2%)

ORIGINAL ARTICLE

# Prospective Study of the Incidence and Risk Factors of Postsplenectomy Thrombosis of the Portal, Mesenteric, and Splenic Veins

*Konstantinos M. Stamou, MD, PhD; Konstantinos G. Toutouzas, MD, PhD; Panagiotis B. Kekis, MD, PhD; Socrates Nakos, MD; Anthippi Gafou, MD; Andreas Manouras, MD, PhD; Eustathios Krespis, MD, PhD; Stylianos Katsaragakis, MD, PhD; John Bramis, MD, PhD*

**Hypothesis:** Splenectomy is recognized as a cause of portal, mesenteric, and splenic vein thrombosis. The exact incidence of the complication and its predisposing factors are not known.

**Design:** Prospective observational cohort study. The median follow-up time of the patients was 22.6 months.

**Setting:** University surgical clinic in a teaching hospital.

**Patients:** A total of 147 consecutive patients who underwent splenectomy in a 4-year period were enrolled in the study.

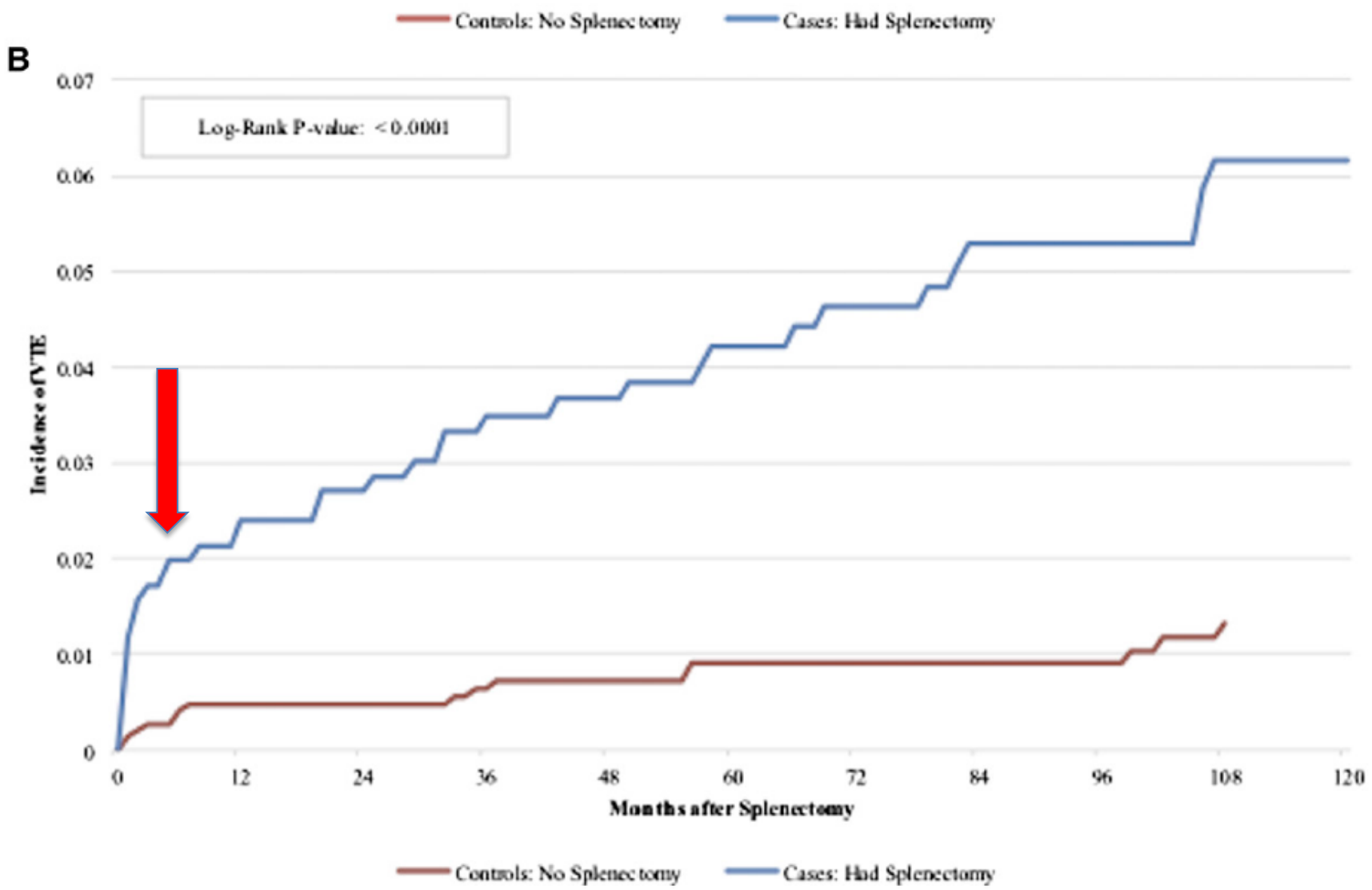
**Interventions:** Preoperative and postoperative evaluation included ultrasonography with color Doppler flow imaging of the portal system, results of blood coagulation tests, fibrinogen levels, D-dimer levels, and complete blood counts. Operative sheets were recorded and reviewed. When portal system thrombosis (PST) was diagnosed, a complete control for acquired and congenital thrombophilia disorders was obtained.

**Main Outcome Measures:** Primary end points of the study were the assessment of the incidence of postsplenectomy PST and the identification of risk factors for its occurrence.

**Results:** Portal system thrombosis occurred in 7 (4.79%) of 146 patients who underwent splenectomy. The age, sex, type or length of the operation, and use of preoperative and postoperative thromboprophylaxis with low molecular weight heparin did not prove to be significant factors in the occurrence of PST. Platelet count of more than $650 \times 10^3/\mu L$ and greater spleen weight (>650 g) was associated with the development of PST ($P=.01$, $P=.03$). Normal D-dimer levels on diagnosis of the complication showed a negative predictive value of 98%. Two of the affected patients were diagnosed with thrombophilia disorders. In a median follow-up period of 22.6 months, no other case of PST was recorded.

**Conclusions:** Postsplenectomy PST occurs in approximately 5% of patients. Possible risk factors are thrombocytosis, splenomegaly, and congenital thrombophilia disorders.

*Arch Surg. 2006;141:663-669*




*Boyle et al, Blood 2013*

# Conclusions – 1

- Platelet increasing strategies before surgery include HD-Ig, DEX, and TPO-RA
- The administration of platelet transfusions is not warranted
- Postoperative excessive doses of steroids can cause infection, gastrointestinal haemorrhage and delayed wound healing
- Both TPO-RA are effective in inducing a platelet increase with a stable duration of a safe postoperative platelet count.
- In postoperative periods requiring long-term anticoagulation (e.g. cardiovascular or orthopedic surgery) they should be preferred over HD-Ig or steroids.

# Conclusions – 2

- The incidence of thrombosis after surgery (splenectomy) appears higher than that of the overall patients, even though larger studies are needed.
- In this setting LMWH prophylaxis, clinical surveillance, and imaging follow-up are warranted

- Clinical practice in the surgical settings other than splenectomy should be improved.