Idiopathic Thrombocytopenic Purpura: Current Concepts In Pathophysiology And Management

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Terminology adopted by the IWG on ITP (Blood, in press)

- ITP = Primary Immune Thrombocytopenia
- Idiopathic thrombocytopenic purpura no longer used
  - We know that ITPO is an autoimmune disorder
  - Not all patients with ITP have purpura
ITP: Definition

1. **Isolated thrombocytopenia** with otherwise normal CBC and peripheral smear

2. **No other conditions** or factors that may cause thrombocytopenia
Epidemiology: The incidence of ITP in adults increases with age.

Frederiksen and Schmidt. Blood 1999;94(3):909-913
ITP: Pathophysiology

- Role of B cells
- Role of T cells
- Role of dendritic cells (?)
Passive transfer of ITP with ITP plasma

Harrington et al, J Lab Clin Med 38:1, 1951

Biography: Dr. William J Harrington, Sr. (Sept. 21, 1923 - Sept. 4, 1992)

Carl V Moore
B cells in ITP

- Antibody production
- Cytokine secretion (TNF alpha, chemokines)
- Antigen presentation
- Co-stimulatory signals for T cells
Chronic ITP is a Th0/Th1-disease

Semple et al, Blood 1996;87:4245-4254
Th2 and Tc2 changes after rituximab

Oligoclonal T cells turn to polyclonal after rituximab
T cells in ITP

- Cytokine secretion: (IFN-γ, IL-2, IL-10)
- Co-stimulatory signals for B cells
- Co-stimulatory signals for APC cells
- Direct antiplatelet T-cell lysis
- Preferential usage of TCR VB (oligoclonality)
- Loss of appropriate T-cell apoptosis
- Direct megakaryocyte damage (?)
- Decreased Treg number and function

Mechanism of Thrombocytopenia in ITP

Decreased platelet survival
Radiolabeled **autologous** platelets

Impaired platelet production
Production $\approx$ Platelet count / Platelet survival

Heterologous platelets are cleared much faster (minutes-hours)

Most patients have **inappropriately low or normal** rates of platelet production

Antibodies can also damage megakaryocytes in the bone marrow

- Electron micrographs, showing normal megakaryocytes (A) versus the apoptotic damaged megakaryocytes (B, C) present in the bone marrow of patients with ITP

TPO levels in ITP are not or only mildly elevated

Clinical presentation

Often diagnosed on the basis of routine labs if thrombocytopenia is mild.

Signs/symptoms:

- Easy bruising
- Mucocutaneous bleeding
- Life-threatening hemorrhages
Impact of ITP on quality of life in relation to other chronic conditions

All scores range from 0 to 100. Higher scores indicate better health-related quality of life (HRQoL)

Adapted from: Bussel J et al. Presented at: 45th ASH Annual Meeting; Dec 6–9, 2003; San Diego, CA, USA

Data on file, Amgen
The 3 categories of ITP patients

1. Those who must or should be treated.
   - Active bleeding
   OR
   - Platelet count <10 x 10⁹/L

2. Those for whom treatment is controversial.
   - No bleeding or mild bleeding tendency
   AND
   - Platelet count 10–30 x 10⁹/L

3. Those for whom there is no need for treatment except in special circumstances.
   - No bleeding nor bleeding tendency
   AND
   - Platelet count >30 x 10⁹/L
Management of the bleeding patient

**How severe is bleeding?**

- **Life-threatening (eg intracranial haemorrhage, gastric haemorrhage [melena])** → see ‘Emergency treatment’

- **Not life-threatening**
  - Severe (eg metrorrhagia, unstoppable epistaxis) → see ‘Emergency treatment’
  - Mild to moderate (eg petechiae, ecchymoses, gingival bleeding) → see ‘Standard treatment’
Emergency treatment

- Intravenous immunoglobulin
  - 1 g/kg, repeated the following day if the platelet count remains $<50 \times 10^9/L$

- High-dose methylprednisolone
  - 1 g/day for 3 days (not for those with gastric haemorrhage)

- Platelet transfusions
  - 10 U every 4–6 hours or 3 U/hour

- Recombinant activated factor VII (rFVIIa)
  - Anecdotal reports

If not bleeding, when should we treat ITP patients?

- Disease considerations
- Patient considerations
- Treatment considerations
Disease considerations: platelet count and bleeding in ITP

0 = No bleeding
1 = Minimal bleeding after trauma
2 = Spontaneous but self-limited bleeding
3 = Spontaneous bleeding requiring special attention
4 = Severe life-threatening bleeding

Platelet count x 10^3/µL

Disease considerations:
natural history of chronic ITP in adults

- Variable and unpredictable
- Spontaneous remissions ~5-10%\(^1\)
- 85% of patients achieve a platelet count >30 x 10\(^9\)/L without any treatment\(^2\)
- Overall mortality risk relative to the general population 4.2 in those with chronic severe ITP\(^2\)

Patient considerations

- **Risk of fatal haemorrhage greatest in older patients**:¹
  - 0.4% per year in patients <40 years
  - 1.2% per year in patients 40–60 years
  - 13% per year in patients >60 years

- **Energetic lifestyles require ‘safer’ platelet counts**

<table>
<thead>
<tr>
<th>Platelet level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20–30 x 10⁹/L</td>
<td>Platelet &gt;20–30 x 10⁹/L</td>
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<tr>
<td>&gt;50 x 10⁹/L</td>
<td>Platelet &gt;50 x 10⁹/L</td>
</tr>
<tr>
<td>&gt;80 x 10⁹/L</td>
<td>Platelet &gt;80 x 10⁹/L</td>
</tr>
</tbody>
</table>

Treatment considerations

- Only a few treatments are truly evidence based and approved by EMEA
- Long-term side effects for new agents are not currently known
- **Treatment** of ITP may be more dangerous than the disease itself:\footnote{Portielje et al. *Blood* 2001;97:2549–2554}
  - 6 patients out of 152 died
  - 2 died from haemorrhage
  - 4 died from infections probably treatment related
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:
  - Vaginal delivery $\geq 50 \times 10^9$/L
  - Caesarean section $\geq 80 \times 10^9$/L

First-line therapy in newly-diagnosed ITP

Corticosteroids
- Prednisone 1–2 mg/kg/day → OR ~70%, sustained responses ~15%¹
- High-dose dexamethasone 40 mg/day for 4 days → ~85% OR, sustained responses >50%²

Early management for those unresponsive to steroids
- IVIg 0.5–1 g/kg/day for 1 or 2 days → OR ~80% (recommended for patients with critical bleeding)¹
- IV anti-D 50–75 μg/kg for 1 day → OR ~70%¹

Splenectomy in ITP

- **Indicated in case of:**
  - Severe thrombocytopenia (Plt <10 x 10⁹/L)
  - High risk of bleeding for Plt counts <30 x 10⁹/L
  - Requirement of continuous glucocorticoid therapy to maintain safe platelet counts

- **CR rate of 66%**

- **Mortality rate with laparoscopic splenectomy 0.2%**

- **Lifelong infection risk**

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Thrombocytopenia-free survival after splenectomy

Defining chronic refractory ITP

The patient has failed to respond to splenectomy AND
The platelet count is <30,000/µL
Long-term outcomes in adults with chronic ITP after splenectomy failure

- 105 patients with refractory ITP; median follow-up 110 months
- 30% patients remained unresponsive to treatment
  - 16% died of ITP (bleeding, 11 patients; therapy complications, 6 patients)
  - 14% died of unrelated causes

Challenges facing clinicians in deciding on treatments for chronic and refractory ITP

- Treatment recommendations derive largely from uncontrolled cohort studies and expert opinion.
- Criteria to define platelet count outcomes are not standardized across studies making their results difficult to compare.
- Important clinical outcomes, such as bleeding and quality of life, are rarely reported in clinical studies.
Management options in chronic refractory ITP

- Simple measures
- Interventional measures*

*Many of which are utilised in an off-label setting
Simple measures

- Look for **accessory spleen**\(^1\)
  - Found in 12% of patients failing to respond
- Look for **H. pylori** at presentation\(^2\)
  - Variable reports of ITP response post-eradication\(^2\)
- **Tranexamic acid**
  - Widely used (no robust evidence)
- **Oral contraceptives**
  - In young women

Interventional measures: non-selective therapies*

- Oral/IV dexamethasone ➔ Osteoporosis, psychosis etc
- IV methylprednisolone ➔ Diabetes, fluid retention
- Danazol ➔ Weight gain, hirsutism, LFTs abnormal
- Dapsone ➔ Haemolysis
- Azathioprine ➔ Immunosuppression, LFTs abnormal
- Vinca alkaloids ➔ Neuropathy
- IV cyclophosphamidine ➔ Leukaemia, cytopenia, teratogenic
- Cyclosporine ➔ Nephrotoxic, immunosuppression
- Combination chemotherapy ➔ Leukaemia, myelosuppression
- Interferon-α ➔ Thrombocytopenia
- Mycophenolate Mofetil ➔ Nausea, diarrhoea

**BUT:** No real evidence of which/when to use or in which order

LFTs, liver function tests;  
Staph, staphylococcal

*Many of which are utilised in an off-label setting  
Interventional measures: targeted therapies

- Thrombopoietin receptor stimulators
- Syk inhibitors
  - R788 (tamatinib fosdium)
- Antibody therapies
  - Campath-1H (anti-CD52)
  - Anti-CD40 ligand (anti-CD154)
  - GMA161 (anti-CD16)
  - Rituximab
- Staphylococcal protein A (PRYX-100)
Rituximab systematic review: Efficacy

19 reports for efficacy (n = 313)

- 150 x 10E9/L: Pooled estimate for response = 46.3%
- 50-150 x 10E9/L: Pooled estimate for response = 24.0%
- >50 x 10E9/L: Pooled estimate for response = 62.5%

Rituximab in chronic ITP

- **No RCT.** Long-term CR in 15–20% of cases
- **Adverse events** mild, but no long-term safety data (>10 year data)
- **Deaths** reported in 2.9% of ITP cases treated with rituximab, but they could not be attributed to the study drug
- Valuable option for patients at high risk for splenectomy and for those not willing to undergo surgery

Autologous haematopoietic stem cell transplantation

- Only one phase I/II study reported
- 14 patients:
  - 5 with Evans’ syndrome
- 6 durable complete responses (9–42 months)
- 2 durable partial responses
- No transplant-related death

Thrombopoietin receptor stimulators

- **Stimulate** platelet production
- **Bind to and activate** TPO-receptors (Mpl)
- **BUT no sequence homology** to TPO
- For two agents, romiplostim and eltrombopag, Phase III studies are complete
- **Long-term** side effects under investigation
- Romiplostim approved by **FDA**
TPO acts through c-Mpl (TPO-receptor)

- TPO acts through c-Mpl (TPO-receptor) to activate signaling pathways.
- Recruitment and phosphorylation of JAK2 and LATENT STAT monomers.
- TPO-R dimerization into the nucleus: binds DNA and activates transcription.
- Histidine 499 involvement.

- SHC, GRB2, SOS, RAS/RAF, MAPK pathways activated.

Stasi et al. Drugs 2008
Romiplostim (nPLate™)

No sequence similarity to natural TPO
Therefore, does not elicit anti-TPO antibodies
Romiplostim in Chronic ITP

- Weekly, s.c. romiplostim in slowly escalating doses (1 µg/kg up to 15 µg/kg) for 24 weeks
- Dose adjusted to achieve a platelet count of 50,000-200,000
- Inclusion criteria: Age ≥18; ITP with platelet count <30,000
- Other treatments were discontinued at least 4 weeks before entry

Kuter DJ et al. Lancet 2008;371:395-403
Dose Adjustments

Target platelet count 50,000-200,000

A

Splenectomised

±SEM

Mean dose (µg/kg)

Study week

B

Non-splenectomised

Mean dose (µg/kg)

Study week

Platelet Counts

A

**Splenectomised**

- **Range = middle 2 quartiles**

B

**Non-splenectomised**

Definition of durable response rate

Platelets $\geq 50,000/\mu\text{L}$ for at least 6 of the last 8 weeks of treatment
Romiplostim efficacy

### Adverse Events

<table>
<thead>
<tr>
<th>Placebo (n=41)</th>
<th>Romiplostim (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Romiplostim</strong></td>
</tr>
<tr>
<td><strong>Severe or life-threatening bleeding</strong></td>
<td>5/41 (12%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>1 ICH 1 PE</td>
</tr>
<tr>
<td>Increased bone marrow reticulin</td>
<td>1 (reversible)</td>
</tr>
</tbody>
</table>

*Because no statistically significant difference between splenectomised and non-splenectomised patients was recorded, the results for this analysis were pooled.

Table 3: Adverse events occurring in at least 10% of patients in either treatment group*

Eltrombopag

Kuter DJ. Blood 2007;109:4607
Eltrombopag for Chronic ITP

Primary end point: Platelet count $\geq 50,000$/mcl by day 43

Randomized Double-blind Phase 2 Trial (n = 118)

- Placebo (n = 29)
- Eltrombopag 30 mg PO once daily (n = 30)
- Eltrombopag 50 mg PO once daily (n = 30)
- Eltrombopag 75 mg PO once daily (n = 28)

Eltrombopag efficacy

Platelet count $\geq 50,000$/mcl by day 43

- Eltrombopag 30 mg: 28%
- Eltrombopag 50 mg: 70%
- Eltrombopag 75 mg: 81%
- Placebo: 11%

Bleeding

- Eltrombopag 30 mg: 17%
- Eltrombopag 50 mg: 7%
- Eltrombopag 75 mg: 4%
- Placebo: 14%

Eltrombopag was effective regardless of concurrent ITP therapy, splenectomy or baseline platelet count

Adverse Events

Mild-moderate headache in all groups including placebo (10-20%)
One 66-yo with COPD and NSCLC died of sepsis after receiving 50 mg eltrombopag for 21 days
No thrombosis reported

Conclusions

Eltrombopag 50-75 mg PO QD is effective for short-term treatment of chronic ITP (≥50,000 platelets in ~80% of patients)
The drug is well tolerated
Significant improvement in bleeding symptoms and quality of life were not well documented in this study
Would a higher dose increase the response rate to 100%?

Long-term Safety and Efficacy of Thrombopoietic Agents are Unknown

<table>
<thead>
<tr>
<th>Table 2. Potential adverse consequences of thrombopoietic growth factor treatment</th>
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<tbody>
<tr>
<td>* Thrombocytosis</td>
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<tr>
<td>Stimulation of tumor cell growth</td>
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<tr>
<td>Stimulation of leukemia cell growth</td>
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<tr>
<td>Interactions with other cytokines</td>
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<tr>
<td>Autoantibody formation</td>
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<tr>
<td>Stem cell depletion</td>
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<tr>
<td>Reduction in threshold for platelet activation</td>
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<tr>
<td>* Increased bone marrow reticulin (positive reticulin stain)</td>
</tr>
<tr>
<td>Increased bone marrow collagen (positive trichrome stain)</td>
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<tr>
<td>Rebound worsening of thrombocytopenia upon stopping treatment</td>
</tr>
</tbody>
</table>

Kuter DJ. Blood 2007;109:4607
ITP: Conclusions

- Both B-cells and T-cell are deranged
- Thrombocytopenia is due both to increased platelet destruction and impaired platelet production
- High-dose DXM probably better than PDN as front-line therapy
- Great efficacy of new thrombopoietic agents in chronic ITP, but long-term safety data are lacking