CURRENT AND EMERGING THERAPIES FOR THE MANAGEMENT OF IMMUNE THROMBOCYTOPENIA

HOWARD A. LIEBMAN, MD
Professor, Medicine & Pathology
University of Southern California-Keck
School of Medicine
Los Angeles, CA

Immune Thrombocytopenia: New Definitions
- Isolated thrombocytopenia (<100,000/mcl) with otherwise normal CBC and peripheral smear.
- Defined as Primary or Secondary by exclusion of associated conditions or factors that can cause thrombocytopenia; ie: Other autoimmune, lymphoproliferative, infectious causes.
- Refractory ITP are only patients who relapse after splenectomy.


Immune Thrombocytopenic Purpura: Pathophysiology
- An autoimmune disorder characterized by accelerated platelet destruction due to phagocytosis of antibody coated platelets by the reticuloendothelial system (RES) in spleen, liver and bone marrow.
- Auto-antibodies (predominantly IgG) are directed against common platelet glycoproteins and, therefore, cross-react with allogeneic platelets.
PLATELET PRODUCTION IN ITP

- Studies have demonstrated the platelet production in ITP is only slightly lower than that observed in normal subjects (39 vs 45 X 10^3/mL per 24 hours). However, 30 to 40% of patients have significantly reduced platelet production.
- Clinical studies have suggested that refractory patients, in particular, have decreased effective platelet production.


Prednisone Therapy in ITP

<table>
<thead>
<tr>
<th></th>
<th>Platelet Count (µL)</th>
<th>Recovery %</th>
<th>Survival (days)</th>
<th>Turnover plts/µL/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>36,000 +/- 12,000</td>
<td>63 +/- 20</td>
<td>2.8 +/- 3</td>
<td>25,000 +/- 17,000</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td></td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>111,000 +/- 42,000</td>
<td>74 +/- 26</td>
<td>3.0 +/- 1.4</td>
<td>57,000 +/- 19,000</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>255,000 +/- 44,000</td>
<td>66 +/- 8</td>
<td>9.6 +/- 0.6</td>
<td>41,000 +/- 5,000</td>
</tr>
</tbody>
</table>

Pathophysiology of ITP

Immune Thrombocytopenia: Diagnosis of Exclusion

- Normal CBC except isolated thrombocytopenia
- Giant platelets on smear, no other cytopenias
- Normal Exam except signs of bleeding
- Secondary ITP: SLE, APS, Thyroid, Evans lymphoproliferative
- Infection: HIV, H Pylori, Hepatitis C

Immune Thrombocytopenia

- Treatment Recommendations
  - Treat only if plt < 20-30k or symptomatic
  - Selection of therapeutic option depends upon:
    A) urgency of platelet increase
    B) tolerated toxicity by patient, ie: steroids
    C) durability of desired effect

Maintenance IV anti-D Therapy: Spontaneous Remissions do Occur

Cooper N et al. Blood 2002; 99: 1922
IgG 75 mg/kg

28 non-splenectomized patients
6 patients off Rx, PLTS > 100,000
6 patients off Rx, PLTS > 30,000
Average cost per patient $7,500
Immune Thrombocytopenia

- **Steroids (1mg/kg q d)**
  - 60-85% response, less 1/3 sustained at 1 year
  - IV IgG 400mg/kg q d x 5 (1g/Kg x 2d)
  - > 75% respond (most transient, < 10% sustained)
- **Anti-RhD (75μg/kg)**
  - Probably similar response to IVIG, immune hemolysis
- **Splenectomy**
  - 60 – 70% sustained remission over 5-10 years
- **Danazol, Vincristine, Colchicine, azathioprine, Cyclophosphamide, Cyclosporin, MMF, many other**
  - *Laparoscopic

RESPONSE TO CORTICOSTEROIDS IN CHRONIC ITP

- Three large studies (250 to 500 patients) of chronic ITP in adults found initial responses to corticosteroid treatment of 65%, 67%, and 71% respectively.
- Median time to platelet count > 100,000/mcl was 7 to 10 days.
- Only 13 to 17% of patients achieved long-term unmaintained remissions.

- Schiavotto C et al. Haematologica 1993; 78(suppl II) 22.

INITIAL TREATMENT OF ITP WITH HIGH-DOSE DEXAMETHASONE

- A prospective uncontrolled trial of 4 days of 40 mg per day of dexamethasone in newly diagnosed patients with platelet count <20 x 10⁹/L or <50 x 10⁹/L with bleeding.
- One hundred and twenty-five patients enrolled, mean age 44 years (range, 17 to 84). Initial mean platelet count 12,200+11,300 mcl (range, 1000 to 48,000 mcl).
- 106/125 (85%) increased platelet counts to >50 x 10⁹/L. 53 (50%) patients relapsed by 6 months.

INITIAL TREATMENT OF ITP WITH HIGH-DOSE DEXAMETHASONE


GIMEMA DEXAMETHASONE TRIAL

- A multicenter trial of high-dose dexamethasone given as 40 mg per day for 4 days every two weeks for 4 cycles only (6 weeks). Response criteria were defined as >150 x 10^9/L for a complete response (CR), >50 to <150 x 10^9/L for a partial response (PR) and >20 to <50 x 10^9/L for minimal response (MR).
- Ninety-five untreated newly diagnosed patients enrolled. All with platelet counts <30 x 10^9/L. Ninety patients were evaluable for response.
- 77 (85.6%) of 90 responded with 58 (64.5%) patients CR.


GIMEMA DEXAMETHASONE TRIAL

GIMEMA DEXAMETHASONE TRIAL

Quality of initial response by age

<table>
<thead>
<tr>
<th>Age</th>
<th>Patients</th>
<th>CR (%)</th>
<th>PR + MR (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 y or older</td>
<td>41</td>
<td>27 (66)</td>
<td>14 (34)</td>
<td>.039</td>
</tr>
<tr>
<td>Younger than 18 y</td>
<td>36</td>
<td>31 (86)</td>
<td>5 (14)</td>
<td>NA</td>
</tr>
<tr>
<td>Younger than 10 y</td>
<td>28</td>
<td>23 (82)</td>
<td>5 (18)</td>
<td>NA</td>
</tr>
<tr>
<td>10 y or older</td>
<td>8</td>
<td>8 (100)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Overall RFS was 81% at 15 months (95% CI: 70.6-92.3). Relapse rate was greater in patients older than 18 years; 9/41 (22%). NA indicates not applicable.

Comparison of first and second rows.
Comparison of third and fourth rows.


GIMEMA DEXAMETHASONE TRIAL

Relapse-free survival by age (A) and initial response (B).


Refractory ITP: Treatment Choices

**Significant Responses**
- Azathioprine, cyclophosphamide
- Intensive chemotherapy: HD cyclophosphamide, CHOP, or BMT
- Mycophenolate mofetil
- Cyclosporin
- Rituximab
- Thrombopoietic agents

**Questionable efficacy**
- Interferon (+ for hepC-ITP)
- IL-11 (neumega)
- Plasmapheresis—(also Staph A)
- Other chemo agents
- Anti-FcR
- Campath-1

Interferon (+ for hepC-ITP)
Summary of Published Studies of Rituximab Treatment of ITP

- 9 studies with 5 or more patients
  - CR+PR Rate: ~50%
  - CR Rate: ~35%

Duration of Response to Rituximab

- Rituximab: 4 x 375 mg/m² weekly for 4 weeks
- Patients were included in this report if their response was documented to be ongoing without additional treatment one year from their first of four infusions whether they were maintaining a response at the time of follow up or had relapsed
- N=44 Patients
  - 44 of 137 (32%) patients had responses to rituximab lasting > 1 year (2 centers in New York and Rome)

Cooper N, et al. Blood 2006;108 (suppl 1) Abst 479

Duration of Response to Rituximab in 20 Splenectomized and 24 Nonsplenectomized Patients with Chronic ITP with Response > 1 year

- Nonsplenectomized: 66.6%
- Splenectomized: 60.0%
RITUXIMAB TO DELAY OR PREVENT SPLENEVTOMY IN ITP.

- A prospective French trial of Rituximab to avoid splenectomy in chronic ITP. Sixty patients enrolled and treated with the standard 4 weekly doses of rituximab.
- Response defined as a platelet count of 50 × 10⁹/L or more at 1 year.


---

RITUXIMAB TO DELAY OR PREVENT SPLENECTOMY IN ITP

- 24/60 (40%) patients had a good response at 1 year. 18/60 (30%) had a complete response with platelets greater than 150 × 10⁹/L.
- Younger patients were statistically more likely to respond at 1 year.
- The response at 1 year was associated with the magnitude of the initial response to rituximab. Patients who had platelet counts 150 × 10⁹/L or more within the first 2 weeks after rituximab infusions, 18 (86%) had good responses at 1 year, while only 6 (40%) of the 15 patients with platelet counts 50 × 10⁹/L or more but less than 150 × 10⁹/L shortly after starting rituximab had good responses at 1 year (P < .01).


---

Thrombopoietin Physiology

Novel Platelet Growth Factors

- Romiplostim (AMG531)
- Eltrombopag
- AKR-501

Romiplostim (AMG 531)

- Unique platform peptibody
- Expressed in E. coli
- Molecular weight = 60,000 D
- 4 Mpl binding sites
- No sequence homology with TPO
- Administered subcu weekly
- Cleared endothelial FcRn (Recycled)
- Cleared RES

Studies With AMG 531 in ITP

- **Phase 1** – Open label study of 24 subjects treated in groups of 4 at 6 dose levels: 0.2, 0.5, 1.0, 3.0, 6.0, 10.0 µg/kg SQ.
- **Phase 2** – Double-blind, placebo-controlled trial of 1 or 3 µg/kg AMG 531 (16 subjects) vs placebo (4 subjects).
- **Phase 3** – Double-blind, placebo-controlled trial of variable doses of AMG 531 vs placebo in patients with or without splenectomy.
- **Extension Study** – Open label safety and efficacy study of long-term weekly treatment of subjects from Phase 1 and Phase 2.

Response: platelets double and ≥50,000

Romiplostim Phase 3 Trials in Chronic ITP

24-Week Treatment Period

- Romiplostim or Placebo (2:1)
- 1 µg/kg starting dose
- Individual dose adjustment based on platelet count weeks 3-24
- Reductions in concurrent ITP therapies allowed when platelet counts > 100 x 10^9/L
- Rescue Medications Allowed


Evaluation of AMG 531 Efficacy in Splenectomized Patients With Chronic Immune Thrombocytopenic Purpura (ITP) in a Randomized Placebo-controlled Phase 3 Study

63 patients enrolled; 42 romiplostim, 21 placebo

- Durable Response
- Overall Response
- Number of Weeks Platelet Response

- Platelet response: platelet count ≥ 50 x 10^9/L
- Durable platelet response: platelet response for ≥ 6 weeks of final 8 weeks, in the absence of rescue medications during 24 week trial
- Overall response: either durable or transient platelet response (≥ 4 weekly platelet responses)

Error bars represent standard deviation of the mean

Proportion of Romiplostim Patients Who Received Rescue Medications

- Patients Receiving Rescue Medications

- Rescue medication: any treatment administered to increase platelet counts

(P = 0.018)
Concurrent Proportion of Romiplostim Patients Who Reduced or Discontinued ITP Therapy - splenectomized

N = number of patients with baseline concurrent ITP therapy
n = number of patients reduced or discontinued

<table>
<thead>
<tr>
<th>Patients Reduced or Discontinued Concurrent ITP Therapy (%)</th>
<th>Placebo</th>
<th>Romiplostim</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 25% Reduction of Concurrent ITP Therapy</td>
<td>0.0</td>
<td>16.7</td>
</tr>
<tr>
<td>Discontinued Concurrent ITP Therapy</td>
<td></td>
<td>66.7</td>
</tr>
<tr>
<td>Reduced or Discontinued Concurrent ITP Therapy</td>
<td>1/6</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Romiplostim: Durable Response and Overall Response
Non-splenectomized CITP

<table>
<thead>
<tr>
<th>Platelet Response</th>
<th>Placebo</th>
<th>Romiplostim</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50 x 10^9/L</td>
<td>46.3</td>
<td>61.0</td>
</tr>
</tbody>
</table>

Durable platelet response: platelet response for ≥ 6 weeks of final 8 weeks; no rescue medications during 24 week treatment
Overall response: either durable or transient platelet response (≥ 4 weekly platelet responses)

Mean (SE) Number of Weeks With Platelet Response
<table>
<thead>
<tr>
<th>Placebo</th>
<th>Romiplostim</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3 (0.8)</td>
<td>15.2 (1.2)</td>
</tr>
</tbody>
</table>

Durable Platelet Response (%)
Overall Platelet Response (%)

Long-term Treatment With Romiplostim Was Continued for 120 Patients (88%)

Did Not Receive Romiplostim: N = 3
- Discontinued study N = 16
- Adverse events n = 4
- Consent withdrawn n = 6
- Death n = 3
- Investigator’s decision n = 1
- Protocol-specified criteria n = 1

Continued Romiplostim: N = 120
- ≥ 24 weeks: 89 patients
- ≥ 48 weeks: 40 patients
- ≥ 72 weeks: 20 patients
- ≥ 120 weeks: 2 patients
Mean Platelet Count Levels Between 50 and 250 x 10⁹/L Over 112 Weeks

- n is the number of patients with available platelet counts, excluding those who received rescue medications.
- Platelet counts within 8 weeks after receiving any rescue medications were excluded.

<table>
<thead>
<tr>
<th>Mean (SE) Platelet Count x 10⁹/L</th>
<th>n = 135</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>89</td>
</tr>
<tr>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>60</td>
<td>33</td>
</tr>
<tr>
<td>70</td>
<td>25</td>
</tr>
<tr>
<td>80</td>
<td>22</td>
</tr>
<tr>
<td>90</td>
<td>16</td>
</tr>
<tr>
<td>100</td>
<td>13</td>
</tr>
</tbody>
</table>

SERIOUS ADVERSE EVENTS

- There were more frequent major bleeding events (event/100 pt/yr) on the placebo arm.
- No difference in thrombotic events between placebo and romiplostim arm. No correlation with platelet count.
- Increased bone marrow reticulum in 10 patients. Appears reversible upon stopping romiplostim and not associated with myelofibrosis.

Eltrombopag

- Small molecule (MW=564)
- Orally bioavailable
- Once daily dosing
- Stimulates megakaryocyte proliferation and differentiation
- Increases platelet counts
- Not immunogenic
- Does not activate platelets
- Active in humans, chimpanzees but no other species

Eltrombopag, an Oral Platelet Growth Factor, for Treatment of Chronic ITP:
A Randomized, Double-blind, Placebo-controlled Trial

- Two Randomized Studies of Eltrombopag in ITP
  - Phase II: 3 dose cohorts of Eltrombopag (30mg, 50mg or 75mg) or placebo for 6 weeks
  - Phase III: 2:1 Eltrombopag 50 mg or placebo for 6 weeks: increase to 75 mg after 3 weeks if platelets <50k
- 117 patients in Phase 2
- 114 patients in Phase 3

Eltrombopag ITP Phase 2 Study

Study design
- Randomized, double-blind, placebo-controlled study

Patient population
- Adults with ITP ≥6 months, having failed at least 1 prior therapy, and platelets <30 x 10⁹/L

Endpoints
- Patients with platelets >50 x 10⁹/L after 6 weeks
- Safety and tolerability

Eltrombopag Phase 2 Results in ITP

Mean platelet count after each week of therapy

- Normal platelet levels

Week 0  | Week 1  | Week 2  | Week 3  | Week 4  | Week 5  | Week 6
--- | --- | --- | --- | --- | --- | ---
Placebo | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo
Eltrombopag 30mg | Eltrombopag 50mg | Eltrombopag 75mg

**Eltrombopag in ITP: Phase II Summary**

Platelet response (p<0.001) with 50 and 75mg
- 70% patients (50mg) and 81% (75mg) achieved platelet counts ≥50,000/µL
- 37% patients (50mg) and 43% (75mg) achieved platelet counts > 200,000/µL

- Trend to reduction in bleeding in 50mg and 75mg arms
- Phase III: 50mg starting dose (up to 75mg after 3 weeks if platelets <50K)


**Long-term Treatment with Eltrombopag: Study Design**

**Efficacy Data**

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count elevation</td>
<td>86/108 (80%)</td>
</tr>
<tr>
<td>Platelet count ≥50 Gi/L at least once during the study</td>
<td></td>
</tr>
<tr>
<td>Durability of platelet count elevation</td>
<td></td>
</tr>
<tr>
<td>Continuous elevation ≥50 Gi/L for ≥10 weeks</td>
<td>43/80 (54%)</td>
</tr>
<tr>
<td>Continuous elevation ≥50 Gi/L for ≥25 weeks</td>
<td>15/63 (24%)</td>
</tr>
<tr>
<td>Effect of retreatment with eltrombopag</td>
<td>45/49 (92%)</td>
</tr>
<tr>
<td>Proportion of prior responders who had a platelet count elevation ≥50 Gi/L during EXTEND</td>
<td></td>
</tr>
<tr>
<td>Concomitant ITP medication reduction</td>
<td>14/40 (35%)</td>
</tr>
<tr>
<td>Subjects who discontinued concomitant ITP medication</td>
<td></td>
</tr>
</tbody>
</table>
Median Platelet Counts (25th and 75th Percentiles) Baseline to Week 20

Splenectomized pts respond as well as non-splenectomized pts

Serious Adverse Events

On therapy (14/109 [13%] patients)
- Hemorrhoidal hemorrhage, chest pain
- Fall
- Dizziness, cellulitis
- Gastroenteritis viral
- Eye injury, cataract traumatic
- Hemolytic anemia
- Kidney infection
- Road traffic accident passenger
- Cholangitis, ALT increase, AST increase, blood bilirubin increase
- Hyperbilirubinemia, anemia, ALT increase
- Pneumonia
- Arthralgia
- Diverticulitis
- Pulmonary embolism

Post-therapy (2/109 [2%] patients)
- Anemia, hypovolemic shock
- Pulmonary embolism

CONCLUSIONS

- Patients presenting with newly diagnosed ITP should be screened for secondary causes since this may modify the approach to treatment (ie: H. pylori, HCV, CLL, LGL).
- More aggressive early interventions may reduce the number of refractory patients and patients requiring splenectomy. New trials should provide proof of this strategy.
- The thrombopoietin receptor agonists provide a new and potentially valuable agent for the management of refractory ITP.