Immune Thrombocytopenia
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2015 Highlights of ASH in Asia
Bangkok, Thailand
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Common Causes of Thrombocytopenia

- Infections
  - Viral including dengue
  - Sepsis, leptospirosis
- Drugs including cytotoxics
- Bone marrow failure
  - Acute leukemia
  - MDS
  - AA
- Liver disease
- Immune mediated
  - Primary (more common)
  - Secondary
Treatment Options in ITP

• First line
  – Steroids (oral prednisone, IV methylprednisolone, high dose dexamethasone)
  – IV Ig

• Second line
  – < 6 months: azathioprine, dapsone, rituximab
  – > 6 months: splenectomy, rituximab
Immune thrombocytopenia: Definition

• Isolated thrombocytopenia (<100 x 10⁹/L) with otherwise normal CBC and peripheral smear

• Disease stages:
  – Newly diagnosed (<3 months)
  – Persistent (3-12 months)
  – Chronic (>12 months)
Why does thrombocytopenia occur in ITP?

• Increased platelet destruction
  – Autoantibodies, cytotoxic B/T-cells
  – Target: platelets

• Impaired platelet production
  – Autoantibodies, cytotoxic B/T-cells
  – Target: megakaryocytes
Mechanism

- Anti-platelet antibody and lymphocytes attack megakaryocyte
- Megakaryocytes undergo apoptosis
- Increase activity of thrombopoietin
ITP: Therapeutic Options

• **Decrease platelet destruction**
  – Decrease platelet clearance by RES
    • Corticosteroids, IV Ig, anti-RhD, splenectomy
  – Inhibit antibody production
    • Corticosteroids, rituximab, mycophenylate, azathioprine, cyclophosphamide, cyclosporine

• **Increase platelet production**
  – TPO receptor agonists
    • Romiplostim, eltrombopag
  – Corticosteroids
Mechanism of Thrombocytopenia

• Fc-dependent vs non-Fc dependent ITP
  – Anti-platelet antibodies present in most ITP
  – Anti IIb/IIIa (80%)
    • Splenic macrophage Fc-mediated destruction
    • Respond to IVIg
  – Anti Ib complex (20%)
    • Not respond well to IVIg
    • Non-Fc mediated destruction by ? mechanism
Fc-independent clearance of platelets

- Anti-GPIbα antibodies in mouse model
  - Crosslink platelet GPIbα
  - Cause platelet activation (↑ P-selectin)
  - Activates neuraminidase (enzyme cleaves sialic acid in blood surfaces)
  - Platelets lose surface sialic acids, removed by Ashwell-Morell receptor on hepatocytes
    - Inhibitors of Ashwell-Morell receptor (asiafetuin) or sialidase (DANA) prevent thrombocytopenia
Ashwell-Morell receptor regulates hepatic thrombopoietin production via JAK2-STAT3 signaling in vivo and in vitro

Renata Grozovsky, Antonija Jurak Begonja, John Hartwig, Herve Falet, and Karin Hoffmeister

• Ashwell-Morell receptors on hepatocytes bind desialylated platelets and provide a novel physiologic feedback mechanism to regulate plasma TPO levels and platelet production in vivo and in vitro

**Diagram:**
- **Hepatocyte**
- **Platelet**
- **Sialic acid**
- **Galactose**
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Loss of sialic acid = desialylation

- sialic acid
- galactose
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- Ashwell-Morell receptors on hepatocytes bind desialylated platelets and provide a novel physiologic feedback mechanism to regulate plasma TPO levels and platelet production in vivo and in vitro.

![Diagram of hepatocyte, platelet, and thrombopoietin interactions](galactose.png)
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• Conclusions:
  – Anti-platelet GPIb antibodies can induce platelet desialylation
    • May need to test patients for antibody type
  – In a mouse model, platelet desialylation led to Ashwell-Morell receptor-mediated platelet clearance in liver
    • Upregulation of basal TPO production
  – RCA-1 (lectin) and anti-Neu 1 (antibody) can identify desialylated platelets
  – Inhibitors of sialidase or Ashwell Morell receptor may be a novel therapy for some ITP patients
Conventional Oral Prednisone Versus High-Dose Dexamethasone for Management of Adult ITP: A Prospective Randomized Multicenter Clinical Trial

Yu Wei, Jingxia Wang, Enqin Yang, Zhengcheng Wang, Yuqi Sang, Zuomo Bi, Cuiai Ren, Fang Zhou Guoquiang Liu, Xin Wang, Jun Peng, Ming Hou

• Prospective randomized multicenter clinical trial
• Newly diagnosed ITP, age ≥ 18 and < 80, PLT < 30 or with bleeding symptoms
• Sustained response: PLT count maintaining above 30 x 10⁹/L for ≥ 6 months
• 1:1 randomization:
  – DXM: 40mg/day PO x 4 days; repeat 4-day course if PLT count remained or dropped below 30 x 10⁹/L by day 10
  – PDN: 1mg/kg/day PO for up to 28 days; then tapered rapidly to dosage <15mg/day in responders or stop in non-responders
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• Conclusions
  – One or two courses of high-dose dexamethasone demonstrated higher CR rate (52.2% vs 28.9%) and shorter time to response (3.21 ± 1.35 vs 5.97 ± 4.28 days) than prednisone
  – High-dose dexamethasone may be a faster first-line choice for adult ITP
  – However, sustained response rates no difference
  – Generally better tolerated than prednisone
Long-term complications after splenectomy in adult chronic ITP with a minimum follow up of 10 years. First results from a single-center case-control study in 140 patients with primary ITP


• Retrospective study

• Inclusion:
  – All primary ITP patients splenectomized more than 10 years ago

• Results:
  – Cumulative incidence of thromboembolic, cardiovascular events was higher in the splenectomized group

• Safety issues?
Successful Discontinuation of Eltrombopag after Complete Remission in Patients with Primary ITP

Tomas Jose Gonzalez-Lopez, Cristina Pascual, Maria Teresa Alvarez-Roman, Fernando Fernandez-Fuertes, Blanca Sanchez-Gonzalez, Isabel Caparros, Isidro Jarque, Maria Eva Mingot, et al.

• Retrospective study
• Spanish Eltrombopag Registry

• Results:
  – 260 patients registered
  – Complete response seen in 201/260 (77%)
  – 80/201 (40%) discontinued treatment
    • 49 evaluable patients
      – 22 had relapse (45%)
      – 26 had sustained response (53%)
      – 1 had sustained response for 10 months but relapsed

• Conclusion:
  – Platelet count response following stopping eltrombopag may be sustained in a small number of patients (~13% of CR patients)
Intravenous Immunoglobulin versus Careful Observation in Children with Newly Diagnosed Immune Thrombocytopenia: First Results of a Randomized Controlled Trial

Katja Heitink—Polle, Masja de Haas, Leendert Porcelijn and Marrie Bruin

Child 3 months – 16 years with
- Newly diagnosed ITP
- PLT count ≤ 20 x 10⁹/L

Web-based randomization:
- Observation OR
- IVIg 0.8g/kg

Clinical parameters
HR QoL questionnaires

Laboratory Studies:
- Basic laboratory studies
- Fcγ receptor polymorphisms
- Regulatory T cells

Short term results:
- Efficacy and safety
- Predictors recovery/response

Long term results:
Chronic ITP: yes/no
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Clinical parameters
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- Basic laboratory studies
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< 72 hours

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<tr>
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<th>IVIg</th>
<th>Observation</th>
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<tr>
<td>1 week</td>
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<tr>
<td>OR:</td>
<td>67/86</td>
<td>33/86</td>
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<td>CR:</td>
<td>59/86</td>
<td>18/86</td>
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<td>77.9%</td>
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<td>68.6%</td>
<td>20.9%</td>
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<td>1 month</td>
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<tr>
<td>OR:</td>
<td>69/86</td>
<td>52/86</td>
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<tr>
<td>CR:</td>
<td>53/86</td>
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<td>61.6%</td>
<td>39.5%</td>
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Overall Response (OR): PLT count ≥ 30 x 10⁹/L; ≥ 2x baseline
Complete Response (CR): PLT count ≥ 100 x 10⁹/L
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• **Conclusion**

  – Although response rate is higher in patients that received IVIg, careful observation is a safe alternative in children with newly diagnosed ITP with spontaneous complete recovery within 1 month in 39.5%.
PETIT 1 and PETIT2: Treatment with Eltrombopag in 171 Children with Chronic Immune Thrombocytopenia


• Study Objectives: safety and efficacy of eltrombopag in subjects (aged 1 to <18 years) from pooled data
• Randomized 2:1 to eltrombopag or placebo
• After the PBO-controlled randomized phase, subjects were permitted to complete 17 or 24 weeks of treatment with open-label EPAG
• Eltrombopag dose: Titrated based on platelet response to a maximum of 75mg daily
• Result:
  – 62% of eltrombopag vs 24% of placebo subjects achieved platelet counts ≥ 50 x 10⁹/L at least once during weeks 1-6
  – Eltrombopag subjects had lower odds of having WHO bleeding grades 1-4 and clinically significant bleeding grades 2-4.
PETIT 1 and PETIT2: Treatment with Eltrombopag in 171 Children with Chronic Immune Thrombocytopenia


• Conclusions:
  – EPAG was safe and raised platelet counts in 62% of pediatric patients with persistent and chronic ITP
  – Platelet count elevations with eltrombopag were durable
    • 47% of subjects had >13 weeks of response during the 24-week eltrombopag-only period
  – Compared with placebo, eltrombopag patients had:
    • Fewer bleeding adverse events
    • Sustained reduction or discontinuation of baseline ITP medications
    • Less rescue medications
Eltrombopag

- first oral, nonpeptide, thrombopoietin receptor agonist (TPO-R) approved for the treatment of chronic ITP
- increases platelet production by binding to the transmembrane domain of the TPO-R and induces proliferation and differentiation of bone marrow progenitor cells in the megakaryocyte lineage
THANK YOU!!!