Immune Thrombocytopenia

David J. Kuter, MD, Dphil
Massachusetts General Hospital

2015 Highlights of ASH in Asia

Bangkok, Thailand

February 28 – March 1

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 10^9/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
    - Cortocisteroids, 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

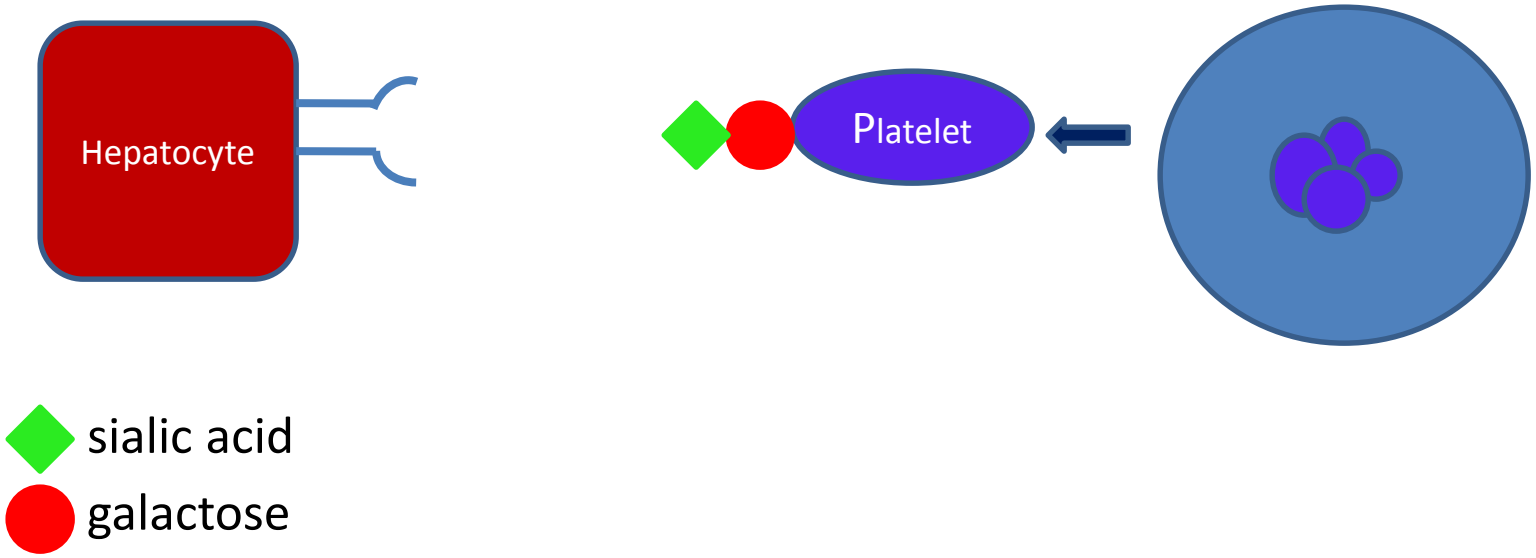
Fc-independent clearance of platelets

- 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

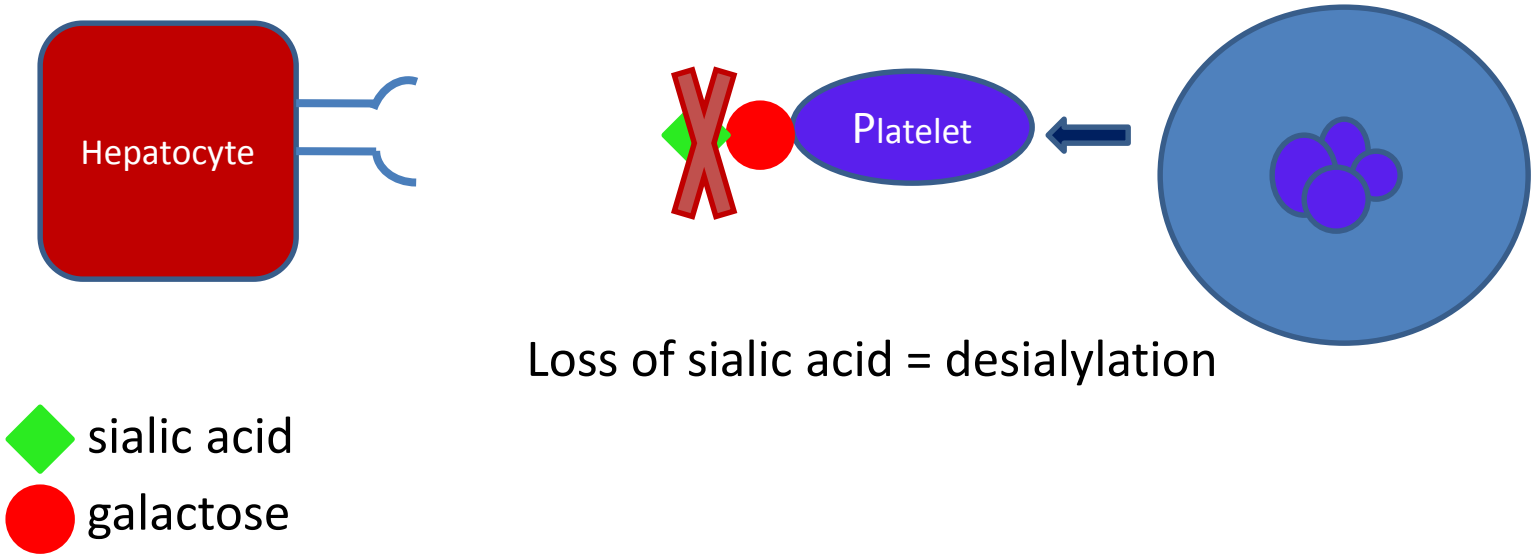
- Ashwell-Morell receptors on hepatocytes bind desialylated platelets and provide a novel physiologic feedback mechanism to regulate plasma TPO levels and platelet productionnin vivo and in vitro



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

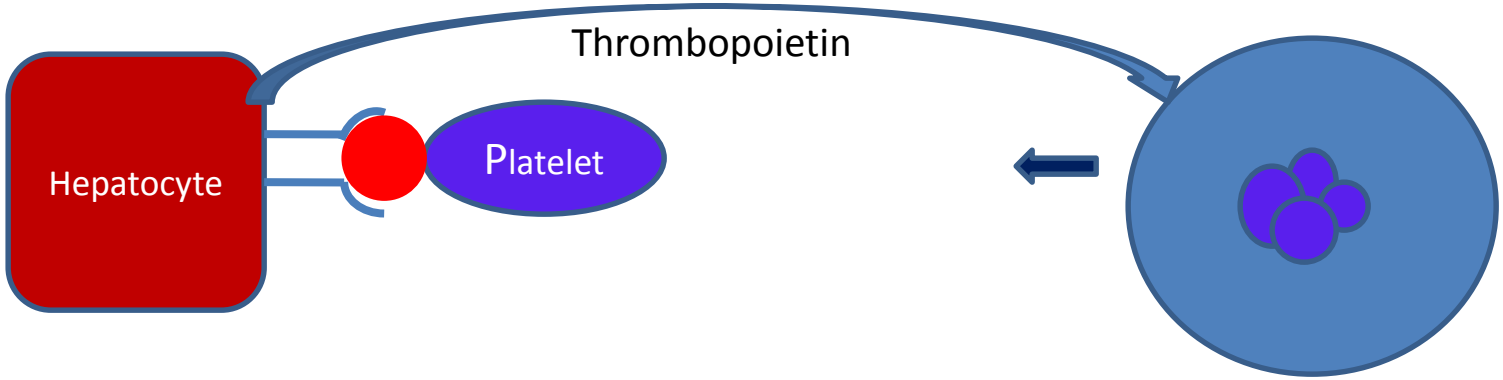
- Ashwell-Morell receptors on hepatocytes bind desialylated platelets and provide a novel physiologic feedback mechanism to regulate plasma TPO levels and platelet productionnin vivo and in vitro



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

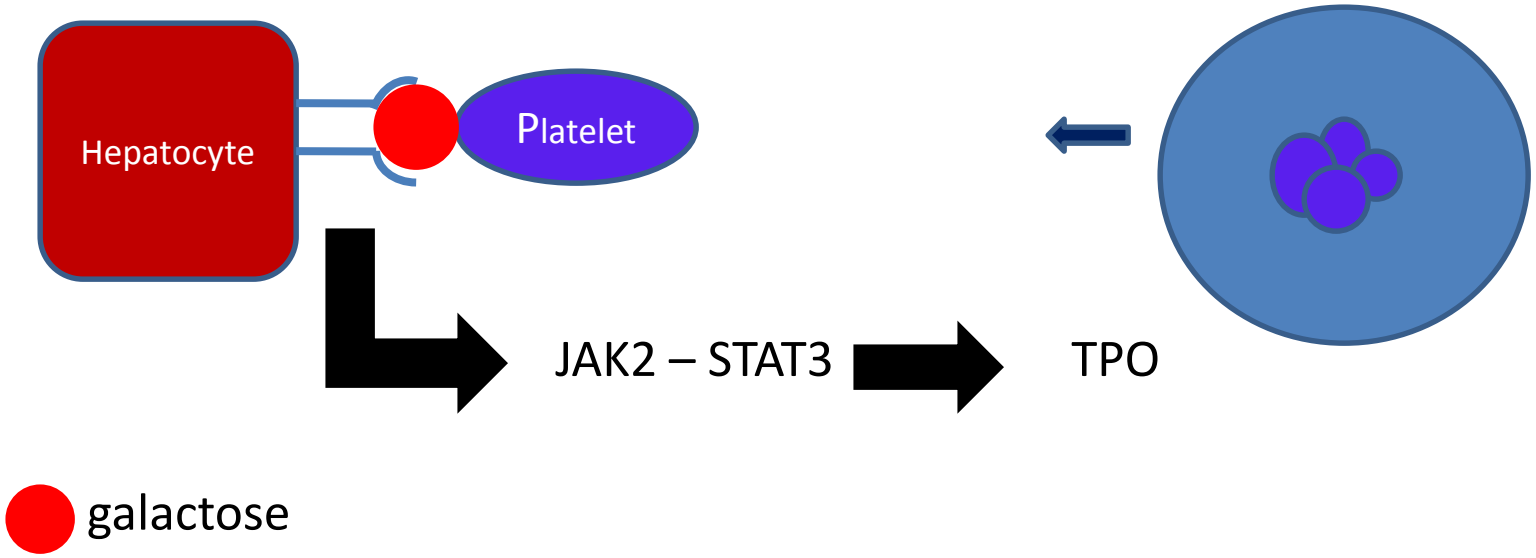


galactose

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



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

- 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 10^9/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 10^9/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

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

- 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

Thai LH, Mahevas M, Roudot-Thoraval F, Languille L, Dumas G, Khellaf M, Haioun C, Bierling P, Michel M, Godeau B

- 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?

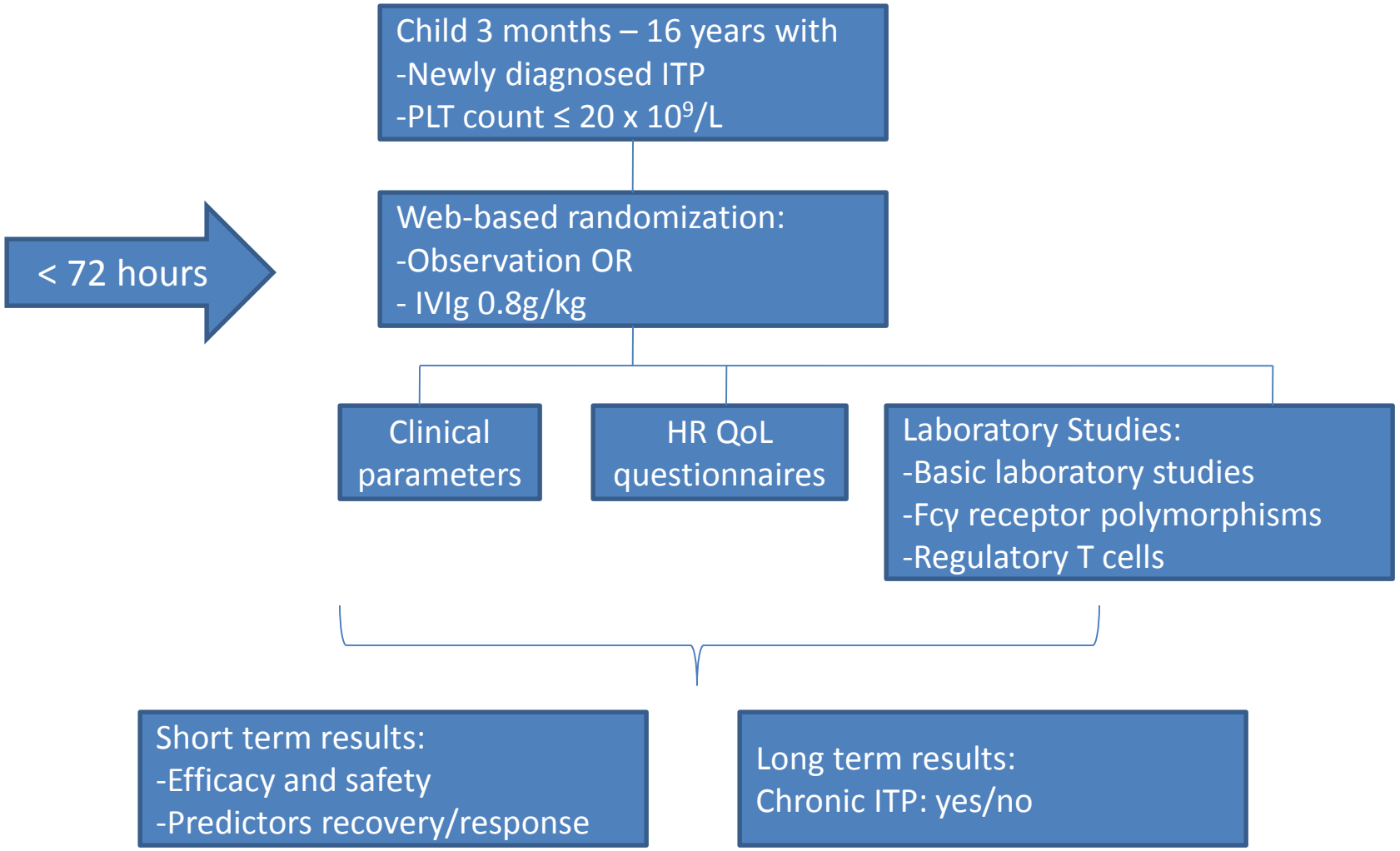
Successful Discontinuation of Eltrombopag after Complete Remission in Patients with Primary ITP

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)

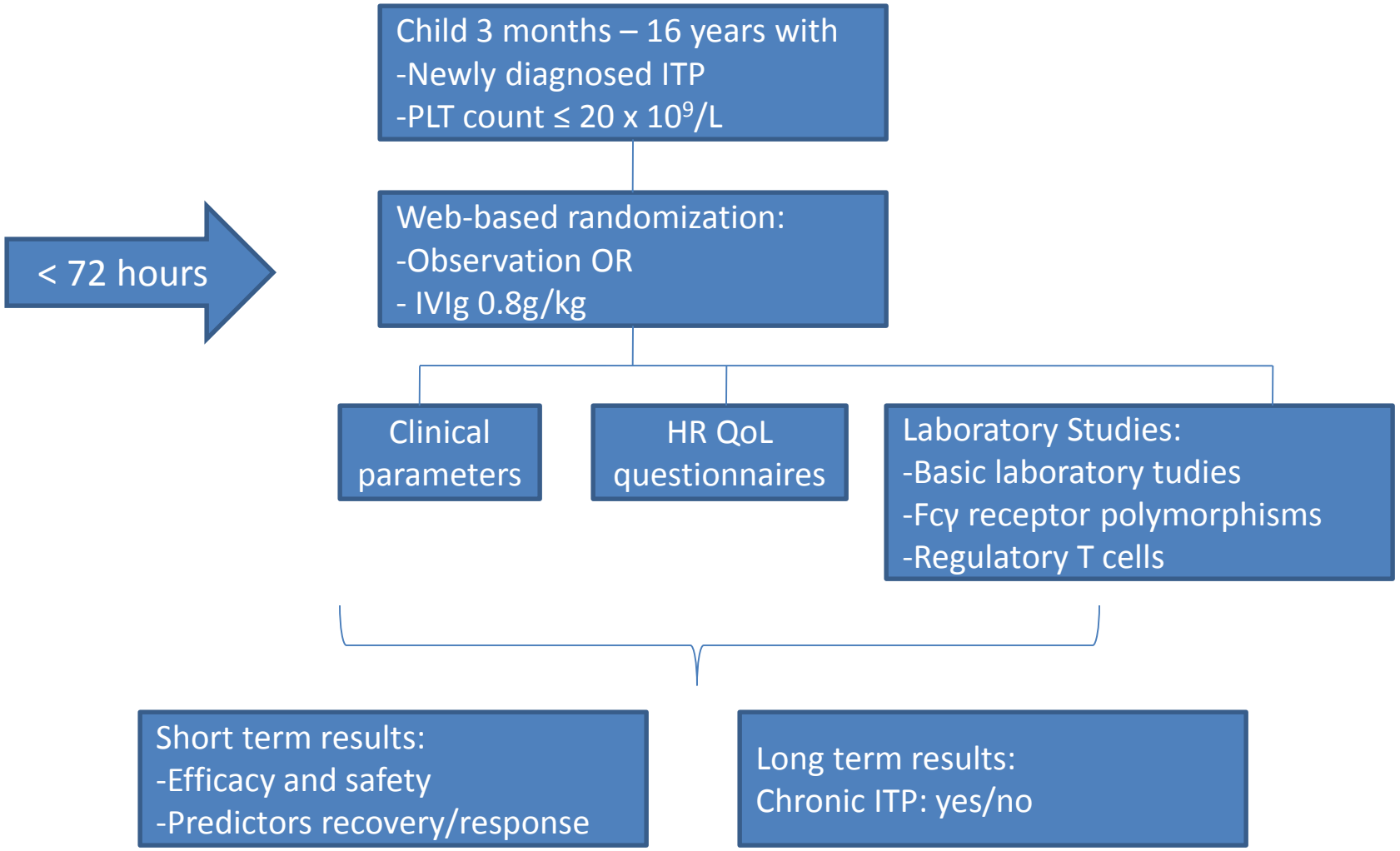
Intravenous Immunoglobulin versus Careful Observation in Children with Newly Diagnosed Immune Thrombocytopenia: First Results of a Randomized Controlled Trial

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



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 Porceljin and Marrie Bruin



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 Porceljin and Marrie Bruin

	IVIg	Observation
1 week	OR: 67/86 77.9% CR: 59/86 68.6%	OR: 33/86 38.4% CR: 18/86 20.9%
1 month	OR: 69/86 80.2% CR: 53/86 61.6%	OR: 52/86 60.5% CR: 34/86 39.5%

Overall Response (OR): PLT count ≥ 30 x 10^9/L; ≥ 2x baseline
Complete Response (CR): PLT count ≥ 100 x 10^9/L

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 Porceljin and Marrie Bruin

- 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

James Bussel, John Grainger, Purificacion Garcia De Miguel, Jenny Despotovic, Franco Locatelli, Thirachit Chotsampancharoen, Elena Donyush, Julian Sevilla Navarro, Bunchoo Pongtanakul, et al.

- Study Objectives: safety and efficacy of eltrombopag in subjects (aged 1 to <18years) 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 10^9/L at least once during weeks 1-6
  - Eltrombopag subjects had lower odds of havig 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

James Bussel, John Grainger, Purificacion Garcia De Miguel, Jenny Despotovic, Franco Locatelli, Thirachit Chotsampancharoen, Elena Donyush, Julian Sevilla Navarro, Bunchoo Pongtanakul, et al.

- 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!!!