Immune Thrombocytopenic Purpura (ITP): Clinical Aspects and Management

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Disclosure Information

• I have no conflicts of interest and nothing to disclose

• I will be discussing the off label use of rituximab, romiplostim, and eltrombopag
Presentation Overview: What’s New in ITP

- Epidemiology
- Diagnosis
- Management
- Outcomes
Epidemiology: The Link of ITP to MMR Vaccine

- Vaccine Safety Datalink from 1991 to 2000
  - 63 children age 12-23 months with ITP
  - 20 (32%) had MMR exposure within the previous 42 days

- Incidence: 2.5 cases/100,000 vaccine doses

- Similar disease duration, platelet count nadir, and outcome between MMR exposed and unexposed children with ITP

- No patients with previous ITP developed recurrence following first MMR vaccination

MMR-Associated ITP: A Systematic Literature Review

- Incidence following natural measles is 10-fold higher than following MMR vaccine
- 0/95 patients with ITP developed a recurrence following first MMR vaccination
  - Safe to give first MMR vaccine
- 2 reports of safe revaccination following MMR associated ITP
  - Check MMR titers
  - If not fully immunized a second dose is recommended

Mantadakis et al, personal communication
Diagnosis: A Review of Criteria

• Diagnostic evaluation

• New terminology
Bone Marrow Evaluation: Yes or No?

- At diagnosis: No
  - Pediatric Oncology Group
  - 2,000 children with ALL: none presented with isolated thrombocytopenia
- Before steroids: Possibly
  - If unable to accurately evaluate the peripheral blood smear or other high risk features
  - Decision analysis showed no benefit to bone marrow biopsy prior to steroids
- Atypical features: Yes
  - Any patient with additional cytopenias or abnormal physical exam findings such as hepatosplenomegaly

Dubansky et al. Pediatrics 1989; 84:1068-71
Anti-Platelet Antibody Testing: Ready for Prime Time?

- Older methods abandoned due to poor sensitivity and specificity

- More recent glycoprotein specific platelet-associated antibody detection
  - Improved specificity (80%) but decreased sensitivity (50%)

- Poor inter-laboratory agreement

Davoren et al., Am J Hematology 2005;78:193-7
Anti-Platelet Antibody Testing

• Not currently indicated in making the diagnosis of ITP

• Might have management implications
  – Prediction of chronic disease
  – Response to medications
  – Association with bleeding severity and impaired platelet function

• More research needed

Fabris et al. Blood 2004;103: 4562-4
Diagnosis: Classic Terminology

- ITP: Immune Thrombocytopenic Purpura
- Diagnostic platelet count: <150,000/mm$^3$
- Duration:
  - Acute: diagnosis to 6 months
  - Chronic ITP: >6 months
Diagnosis: New Proposed Terminology

• International ITP Working Group: Standardization of terminology, definitions, and outcome criteria for ITP

• ITP: Immune Thrombocytopenia Purpura

• Diagnostic platelet count: <100,000/mm³

• Duration:
  – Acute Newly diagnosed: diagnosis to 3 months
  – Persistent ITP: 3 to 12 months
  – Chronic ITP: >12 months

Rodeghiero et al., Blood 2009;113: 2386-93
New Proposed ITP Terminology

• Severity
  – Based on “clinically relevant bleeding”, not platelet count

• Refractory ITP
  – Failed splenectomy or relapsed after splenectomy
  – Definition less clear in children

• Response to treatment
  – Complete response: Platelet count $\geq 100,000/mm^3$
  – Response: Platelet count $\geq 30,000/mm^3$ and $\geq 2$ times baseline
  – Absence of bleeding

• Will physicians adopt these recommended changes?

Rodeghiero et al., Blood 2009;113: 2386-93
Management of ITP

Who and when to treat?

What to treat with?
Who and When to Treat?

Intercontinental Cooperative ITP Study Group (ICIS) Registry II

Founded in 1997
500 physicians from over 60 countries
Over 4000 patients registered on ICIS studies

http://pages.unibas.ch/itpbasel/
ICIS Registry II: Aims

- To determine the frequency, timing, site, and severity of hemorrhage in children with ITP
  - At diagnosis and during the following 28 days
- 863 patients had bleeding severity assessments available at diagnosis and day 28

Neunert et al., Blood 2008;112:4003-8
ICIS Registry II: Bleeding Severity Assessment

1: None or mild - no bleeding at all or bruising, petechiae, occasional mild epistaxis with very little or no interference with daily living

2: Moderate - more severe skin manifestations with some mucosal lesions and more troublesome epistaxis or menorrhagia

3: Severe - bleeding episodes (epistaxis, melena, menorrhagia, and/or intracranial hemorrhage) requiring hospital admission and/or blood transfusion, that is, symptoms interfering with quality of life

Bolton-Maggs and Moon, Lancet 1997;350: 620-3
ICIS Registry II: Bleeding at Diagnosis

<table>
<thead>
<tr>
<th>Bleeding Severity</th>
<th>Median Platelet Count (per mm³)</th>
<th>All Patients (n=863)</th>
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<td>17,000</td>
<td>665 (77%)</td>
<td>505 (74%)</td>
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<td>10,000</td>
<td>173 (20%)</td>
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<td>9,000</td>
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*1 non-fatal intracranial hemorrhage (ICH)

Neunert et al., Blood 2008;112: 4003-8
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Neunert et al., Blood 2008;112: 4003-8
ICIS Registry II: New Hemorrhage During the Following 28 Days

863 Evaluable Patients

665 No or Mild Bleeding at Diagnosis

505 Platelet Count <20K

- 3 (0.6%) Developed Severe Bleeding
- 9 (1.8%) Developed Moderate Bleeding

160 Platelet Count >20K

- 0 Developed Severe Bleeding
- 1 (0.6%) Developed Moderate Bleeding

Neunert et al., Blood 2008;112: 4003-8
ICIS Registry II: Conclusions

• Severe bleeding following diagnosis:
  – IVIG: 1/146
  – Corticosteroids: 0/113
  – Anti-D immunoglobulin: 0/65
  – Combined therapy: 0/8
  – No drug therapy: 2/138

• No relationship between the initial therapy and development of severe bleeding (p=0.82)

• Conduct of a superiority or non-inferiority treatment study using reduction in severe hemorrhage as the primary outcome is NOT feasible

Neunert et al., Blood 2008;112: 4003-8
What to Treat With?

- Newly diagnosed ITP
  - Observation
  - Corticosteroids
  - Intravenous immunoglobulin
  - Anti-D immunoglobulin

- Persistent or chronic ITP
  - Splenectomy
  - Rituximab
  - Immunosuppression
  - TPO-like agents
What to Treat With?

• Newly diagnosed ITP
  – Observation
  – Corticosteroids
  – Intravenous immunoglobulin (IVIG)
  – Anti-D immunoglobulin

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Severe Refractory ITP: Survey of Physician Recommendations

• Survey of ASPHO physicians
• Management recommendations for a patient with chronic ITP (1 year), major bleeding, and impaired quality of life
  – 35% return rate
  – 130 (44%) would recommend rituximab
  – 96 (33%) would recommend splenectomy
  – 64 (22%) would recommend additional therapies
    • Observation, high dose corticosteroids, vincristine, 6-mercaptopurine, and other immunosuppression

Neunert et al., Pediatr Blood Cancer 2008;51: 513-6
Severe Refractory ITP: Survey of Physician Recommendations

- Decision to recommend splenectomy influenced by:
  - Concerns about the long-term risk of sepsis
  - The irreversible nature of splenectomy
  - The possibility of spontaneous remission without splenectomy

- 75% did not feel splenectomy offered the only chance of cure

Neunert et al., Pediatr Blood Cancer 2008;51:513-6
Rituximab for Chronic ITP

• 36 patients enrolled on the prospective Phase 1/2 trial
  – Median age 11.2 years
  – 11/36 (31%) had platelet count >50,000/mm³ for 4 consecutive weeks
  – Median time to response 1 week (range 1-7 weeks)

• One year follow-up data
  – 8/11 (72%) had a sustained response >150,000/mm³

• Overall 22% of treated patients had a platelet count >150,000/mm³ at 12 months

Bennett et al., Blood 2006;107:2639-42
Rituximab for Chronic ITP

• Retrospective review of 49 patients
  – Median age 10.7 years
  – 34/49 (69%) had platelet count $>50,000/mm^3$ for at least 7 days
  – Median time to response 8.5 days (range 2-120 days)

• 21/49 (43%) of patients had platelet count $>50,000/mm^3$ at median follow-up 20.2 months

• Factors predictive of a platelet count $>50,000/mm^3$
  – Unrelated to age, sex, platelet count at diagnosis, or previous splenectomy
  – Duration of disease was shorter in patients who responded

Parodi et al., Br J Haem 2009;144:552-8
Limitations of Rituximab

• No dosing studies available
  – Possible that we are overdosing

• Not benign therapy
  – Serum sickness, infection risk, and infusion reactions

• May take time to have a response
  – Not appropriate for child with acute bleeding

• Long-term remission rate is less than with splenectomy

Taube et al., Haematologica 2005;90:281-2
Thrombopoietic (TPO-like) Agents

- Romiplostim (Nplate): SQ weekly
- Eltrombopag (Promacta): PO daily

- Both effective in adults with refractory ITP at increasing platelet count
- Increased platelet count usually by 2 weeks
- Headache most common side effect
- Elevated liver enzymes with Eltrombopag
- Reports of patients developing increased bone marrow reticulin
- Thrombosis rare and usually associated with comorbidities
Limitations of TPO-like Agents

- No pediatric data
- Difficult administration
  - Eltrombopag: dietary restrictions
  - Romiplostim: given in physician’s office
- Cost
  - Eltrombopag: 50 mg tabs $3,300
  - Romiplostim: 500 mcg vial $2,656
- Long-term side effects still need to be established
- Not curative therapy
  - In most cases platelet count returns to baseline or below within 2 weeks of drug discontinuation
Evaluating Patient - Related Outcomes

• Platelet count is historically used as a surrogate end-point in ITP research and patient management

• Does the platelet count reflect severity of disease?

• Medications may have effects beyond the platelet count
  – Steroids may stabilize the vascular endothelium and reduce bleeding prior to an increase in platelet count
Looking Beyond the Platelet Count: Additional Outcomes

• Therapy related
  – Adverse effects of drug therapy
  – Costs of therapy (direct and indirect)

• Patient experiences
  – Bleeding severity
  – Health-related quality of life
Medication Side Effects

- Underemphasized or not quantified
- Frequency, severity, and time course unknown
- Steroids:
  - Moodiness, weight gain, irritability, bone pain, hypertension, and hyperglycemia
- IVIG:
  - Aseptic meningitis, headache, and infusion fever and chills
- Anti-D immunoglobulin:
  - Hemolytic anemia, DIC, fever and chills
- Rituximab:
  - Infusion reactions, increased risk of infection, serum sickness
- Side effects of additional immunosuppression
Cost Analysis of Treatment of a Newly Diagnosed Child

- Anti-D immunoglobulin, IVIG, and steroids (PO and IV) for a 20 kg child with newly diagnosed ITP were compared

- Assumptions:
  - Hospitalized until platelet count >20,000/mm³
  - No re-treatment needed
  - Time lost from work of one parent
  - 0.1% risk of ICH per hospital day

- Did not include:
  - Rare, but severe side effect risks
  - Bone marrow performed prior to corticosteroid administration
  - The option of observation without treatment

Cost Analysis Results

• IVIG and IV corticosteroids found less effective and more expensive than anti-D immunoglobulin and oral corticosteroids

• Comparison between anti-D immunoglobulin and oral corticosteroids
  – In order to gain one day without severe thrombocytopenia and presumed risk of ICH it costs $7,616 to give anti-D instead of corticosteroids
  – $21,000 without hospitalization

Bleeding Severity Assessment: Why is it Important?

- No standard means to measure amount of bleeding
- Important since bleeding can be different from that predicted by platelet count
- Patients don’t know their platelet count at any given moment
- Important determinant of treatment decisions
<table>
<thead>
<tr>
<th>First Author, Year of Publication</th>
<th>Measure</th>
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<tbody>
<tr>
<td>Lacy, 1977</td>
<td>0-4</td>
</tr>
<tr>
<td>Buchanan, 1984</td>
<td>0-4</td>
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<td>Blanchette, 1993</td>
<td>Moderate and Severe</td>
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<td>Bolton- Maggs and Moon, 1997</td>
<td>None, Mild, Moderate, Severe</td>
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<td>Sutor, 2001</td>
<td>Minor, Major, Death</td>
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<tr>
<td>Godaeu, 2002</td>
<td>31 point scale</td>
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<td>Buchanan, 2002</td>
<td>0-4 Site Specific</td>
</tr>
<tr>
<td></td>
<td>0-5 Overall</td>
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<tr>
<td>Paige, 2007</td>
<td>0-2 Site Specific</td>
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<tr>
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Limitations of Current ITP Bleeding Assessment Methods

• Not designed with rigorous methodology
  – Investigators arbitrarily determined clinically relevant bleeding
  – Minimal validity and reliability testing
  – Did not account for parents and patient perspective

• Included medical interventions

• Multiple site-specific scores are difficult to apply to research design
  – Need to assess sites of bleeding individually, but also have one score that reflects overall bleeding
Health-Related Quality of Life

• Addresses what patients are most concerned with at the end of the day
• Accounts for impact of the disease on the daily activities of the patient
• Explores factors that might not be apparent to physicians at the time of the visit
• May differ depending on the disease state: The longer you live with something the more or less it may bother you
Health-Related Quality of Life: The KIT Questionnaire

• The Kids’ ITP Tool (KIT)
  – The first ITP specific quality of life measure for children
  – 26 item questionnaire

• Questionnaire applied in different settings
  • Patient questionnaire - children >7 years
  • Parent questionnaire
  • Parent proxy questionnaire

• Has undergone validity and reliability testing
• Needs to be applied prospectively in a large cohort of ITP patients

Health-Related Quality of Life: Examples from the KIT

- Examples:
  - I was bothered…….
    - because I could not do the activities I like
    - because I could not do anything to get better
    - by my bruises
    - the changes in how I looked
    - because I had to stay overnight in hospital
    - I had to take medicine
  - I was worried…….
    - about my platelet count
    - about my ITP getting worse
    - about having a more serious disease
Putting it All Together: The Impact of ITP on the Patient

**Benefit**
- Rise in Platelet Count
- Possible Reduction in Bleeding
- Ability to Return to Activities
- Improved Health Related Quality Life

**Risk**
- Adverse effects
- Costs
- Inconvenience

**Desired Outcome**
A Healthy and Happy Child
Questions?