Management of Immune Thrombocytopenic Purpura (ITP) in Children

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University of Illinois College of Medicine
Peoria, IL

Provided as an educational service by Cangene bioPharma
Management of ITP in Children

This educational program, provided as a service by Cangene bioPharma, is designed for healthcare professionals who treat children. Featuring Dr. Michael Tarantino, the Medical Director of the Bleeding and Clotting Disorders Institute and Professor of Pediatrics and Medicine at the University of Illinois College of Medicine – Peoria, this presentation provides guidance on the diagnosis, management and treatment of pediatric ITP.

The objectives of this program are to

- Understand the pathophysiology of ITP
- Recognize the signs and symptoms of ITP
- Become familiar with recommended first-line therapies
- Understand the risks and benefits of recommended first-line therapies
Overview of Pediatric ITP

- Triggers of ITP are not entirely known
- Major or minor bleeding is difficult to predict, but severe bleeding is uncommon
- Drugs used to treat ITP work in a variety of ways and have characteristic side effect profiles
- ITP commonly resolves spontaneously in children, less commonly in adults

Pathophysiology
Autoimmune-Driven Processes

ITP Symptoms

For a more detailed presentation on this topic, visit the Platelet Disorder Support Association (PDSA) website at http://store.shoppdsa.org/394.html to purchase "Pathophysiology of ITP and Current Therapies" DVD.

Spectrum of Disease

Diagnosis

Please see Important Risk Information and Boxed Warning on pages 18-19.
Please see accompanying full Prescribing Information for full prescribing details.
Which Children are Likely to Have Serious Bleeding?

- Wet purpura
- Aspirin users
- Head trauma
- Low platelet count (<10,000/mm³)
  - "permissive but not sufficient evidence"
  - About 3/4 of children with serious bleeding had a platelet count <10,000/mm³


Diagnosis of ITP

- Isolated thrombocytopenia with associated purpura
- Diagnosis of exclusion
  - Look for enlarged spleen, liver, and lymph nodes

Classification of ITP

- Traditional
  - Acute (<6 months’ duration)
  - Chronic (>6 months’ duration)
- 2010 International Consensus Guidelines
  - Newly diagnosed
  - Persistent (3-12 months’ duration)
  - Chronic (>12 months’ duration)

First-Line Therapy

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<table>
<thead>
<tr>
<th>First-Line Therapy: IVIG</th>
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<tbody>
<tr>
<td>- Rapid platelet response</td>
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<tr>
<td>- Plasma-derived</td>
</tr>
<tr>
<td>- 3+ hour infusion time</td>
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<tr>
<td>- Expensive</td>
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<tr>
<td>- Side effects</td>
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<tr>
<td>- Infusion reactions</td>
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<tr>
<td>- Headache, fever, chills, nausea</td>
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<tr>
<td>- Rare complications</td>
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<tr>
<td>- Aseptic meningitis</td>
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<tr>
<td>- Kidney impairment or failure</td>
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<td>- Hemolytic anemia</td>
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<table>
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<tr>
<th>First-Line Therapy: IV Anti-D Immune Globulin</th>
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<tr>
<td>- Plasma derived</td>
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<tr>
<td>- Infused in 3-5 minutes</td>
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<tr>
<td>- Platelet response may be dose related</td>
</tr>
<tr>
<td>- Side effects</td>
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<tr>
<td>- Infusion reactions</td>
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<tr>
<td>- Headache, fever, chills, nausea</td>
</tr>
<tr>
<td>- Hemolytic anemia</td>
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<tr>
<td>- Mean decrease in hemoglobin usually &lt;2 g/dL</td>
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<tr>
<td>- Hemoglobin decrease ≥2 g/dL has rarely been associated with renal failure and DIC</td>
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Monitor patients for 8 hours post-infusion for signs and symptoms of IVH. Use another agent if patient has autoimmune hemolytic anemia with pre-existing hemolysis, renal impairment or +DAT.

<table>
<thead>
<tr>
<th>First-Line Treatment of Pediatric ITP: 2010 International Consensus Guidelines</th>
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<tbody>
<tr>
<td>- Anti-D (if Rh+) nonsplenectomized,</td>
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<tr>
<td>- 50-60 µg/kg x 1</td>
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<tr>
<td>- IVIG</td>
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<tr>
<td>- 0.8-1 g/kg x 1-2 doses</td>
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<tr>
<td>- Corticosteroids</td>
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<td>- Prednisone, 1-2 mg/kg/day, taper off in ≤3 weeks</td>
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Please see Important Risk Information including Boxed Warning at the end of this presentation.

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<tr>
<th>First-Line Therapy: Corticosteroids</th>
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<tr>
<td>- Inexpensive</td>
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<tr>
<td>- Side effects may be treatment limiting and include</td>
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<tr>
<td>- Avascular necrosis</td>
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<tr>
<td>- Diabetes</td>
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<td>- Gastrectomy, ulcers</td>
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<tr>
<td>- Growth retardation</td>
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<tr>
<td>- Hypertension</td>
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<tr>
<td>- Insomnia</td>
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<tr>
<td>- Personality changes</td>
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<tr>
<td>- Opportunistic infection</td>
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<tr>
<td>- Most side effects are dose and duration dependent</td>
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<tr>
<td>- Platelet counts decrease immediately after therapy is discontinued</td>
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How I Manage Pediatric ITP

- Establish diagnosis of ITP
  - Treat if:
    - Wet purpura
    - Platelets <10,000/µL
    - Lack of access to emergency care
  - Observe if:
    - Dry purpura only
    - Platelets >20,000/µL
    - Reliable caregivers
    - Ready access to emergency care

*Rationale for Continued Use of WinRho® SDF (Rh(D) Immune Globulin Intravenous (Human))*

- Only anti-D licensed for pediatric use
- Overall response rates in acute ITP
  - Increases in platelet levels after 1 and 3 days
- Overall response rates in chronic ITP
  - Average duration of response is 30 days
- Dose can be adjusted based on response and hemoglobin level

“IV anti-D may be an effective alternative to IVIG as it can be infused in a shorter time, is produced from a smaller donor pool and has a potentially longer response…”


*Intended solely as a guideline.

Please see accompanying full Prescribing Information for full prescribing details.
Response Rates in Children with Chronic ITP

WinRho SDF Liquid is Bioequivalent to WinRho SDF Lyophilized
In two companies' pharmacokinetic studies (N=101), the formulations were bioequivalent following IV administration based on the area under the curve to 84 days and had comparable pharmacokinetics following IM administration. Both formulations also had similar elimination half-lives. WinRho SDF must be administered via the intravenous route for the treatment of ITP.

WinRho SDF has a Safety and Tolerability Profile Established in Clinical Trials
- In clinical trials, 7% of WinRho infusions had at least 1 adverse reaction – The most common adverse reactions were: headache (2%), chills (<2%) and fever (1%), which are expected adverse drug reactions following intravenous administration of human immune globulins

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Conclusion

• Pediatric ITP may range in severity from asymptomatic to mucocutaneous bleeding to intracranial hemorrhage
  - Often resolves spontaneously
• Diagnosis of exclusion
  - Bruising and petechiae are common symptoms
• 2010 International Consensus Guidelines recommends anti-D immune globulin, MIG and corticosteroids as first-line therapy
• WinRho® SDF (Rh(D) Immune Globulin Intravenous [Human]) remains a beneficial first-line therapy in the treatment of pediatric ITP

For a more detailed presentation on the pathophysiology and treatment of ITP, visit the Platelet Disorder Support Association (PDSA) website at http://store.shoppdsa.org/394.html to purchase the "Pathophysiology of ITP and Current Therapies" DVD.

Thank you.

WinRho® SDF is a registered trademark of Cangene Corporation. Manufactured by Cangene Corporation. Distributed by Cangene bioPharma, Inc. © 2011 Cangene Corporation. All rights reserved. CBI-WR-PLLVID-2011-02

Please see Important Risk Information and Boxed Warning on pages 18-19.
Please see accompanying full Prescribing Information for full prescribing details.
Indications and Important Risk Information

Indications and Usage
WinRho® SDF [Rho(D)] Immune Globulin Intravenous (Human) must be administered via the intravenous route when used in clinical situations requiring an increase in platelet count to prevent excessive hemorrhage in the treatment of non-splenectomized, Rho(D)-positive:

• children with chronic or acute ITP,
• adults with chronic ITP,
• children and adults with ITP secondary to HIV infection.

The safety and efficacy of WinRho SDF has not been evaluated in clinical trials for patients with non-ITP causes of thrombocytopenia or in previously splenectomized patients or in patients who are Rho(D)-negative.

WinRho SDF Liquid is Bioequivalent to WinRho SDF Lyophilized

In two comparative pharmacokinetic studies (N=101), the formulations were bioequivalent following IV administration based on the area under the curve to 84 days and had comparable pharmacokinetics following IM administration. Both formulations also had similar elimination half-lives. WinRho SDF must be administered via the intravenous route for the treatment of ITP.

Important Risk Information

ANGER: INTRAVASCULAR HEMOLYSIS (IVH)

• Intravascular hemolysis (IVH) leading to death has been reported in patients treated for immune thrombocytopenic purpura (ITP) with WinRho SDF.
• IVH can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress syndrome (ARDS).
• Serious complications including severe anemia, acute renal insufficiency, renal failure and disseminated intravascular coagulation (DIC) have also been reported.

Closely monitor patients treated with WinRho SDF for ITP in a healthcare setting for at least 8 hours after administration. A dipstick urinalysis to monitor for hematuria and hemoglobinuria is to be performed at baseline and then after administration at 2 hours, 4 hours and prior to the end of the monitoring period. Alert patients and monitor the signs and symptoms of IVH including back pain, shaking chills, fever, and discolored urine or hemoglobinuria. Absence of these signs and/or symptoms of IVH within 8 hours do not indicate IVH cannot occur subsequently. If signs and/or symptoms of IVH are present or suspected after WinRho SDF administration, posttreatment laboratory tests should be performed including plasma hemoglobin, haptoglobin, LDH, and plasma bilirubin (direct and indirect).

For use in the treatment of ITP, do not use WinRho in:

• Patients who have had known anaphylactic or severe systemic reaction to the administration of human immune globulin products.
• IgA deficient patients with antibodies to IgA and a history of hypersensitivity.
• Patients with autoimmune hemolytic anemia, with pre-existing hemolysis or at high risk for hemolysis.
• Infants for the suppression of Rh(D) isoimmunization.

The liquid formulation of WinRho SDF contains maltose. Maltose in IGIV products has been shown to give falsely high blood glucose levels in certain types of blood glucose testing systems. Due to the potential for falsely elevated glucose readings, only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in patients receiving WinRho SDF Liquid.

WinRho SDF is made from human plasma. It may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The safety and efficacy of WinRho have not been evaluated in clinical trials for patients with non-ITP causes of thrombocytopenia or in previously splenectomized patients or in patients who are Rho(D)-negative.

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur upon use of Immune Globulin Intravenous (IGIV) products, including WinRho SDF. Ensure that patients are not volume depleted before administering WinRho SDF. For patients at risk of renal dysfunction or failure, including those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs, administer WinRho SDF at the minimum infusion rate practicable.

In Rho(D)-positive patients with ITP, side effects related to the destruction of Rho(D)-positive red blood cells, most notably decrease hemoglobin, can be expected. In most cases, the red blood cell destruction is believed to occur in the spleen. Thrombotic events may occur following treatment with WinRho SDF and other IGIV products.

Noncardiogenic pulmonary edema [Transfusion-related Acute Lung Injury (TRALI)] may occur in patients following IGIV treatment.

General adverse reactions associated with the use of WinRho SDF include body weakness, abdominal or back pain, low blood pressure, paleness, diarrhea, abnormal blood work, joint pain, muscle pain, dizziness, abnormal movement, sleepiness, itchiness, rash, and sweating. In the treatment of ITP, the most common adverse events (≥2% of infusions) were headache, chills, and fever.
Supporting platelets and patients for more than 15 years

• **WinRho® SDF** [Rh(D) Immune Globulin Intravenous (Human)] has a safety and tolerability profile established in clinical trials and 15 years of use

• In a pivotal trial (N=146), there was no significant difference in response rates between **WinRho** [Rh(D) Immune Globulin (Human) for Injection] (84.2%), low-dose IVIG (90.0%), or high-dose IVIG (93.1%)¹,²†

• In children with chronic ITP, a response rate of 79% was observed with **WinRho**¹,²‡

• The mean duration of response in children with chronic ITP was 36.5 days¹§

**WinRho SDF Liquid Is Bioequivalent to WinRho SDF Lyophilized¹**
In two comparative pharmacokinetic studies (N=101), the formulations were bioequivalent following IV administration based on the area under the curve to 84 days and had comparable pharmacokinetics following IM administration. Both formulations also had similar elimination half-lives. **WinRho SDF** must be administered via the intravenous route for the treatment of ITP.

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