Beyond Plasma Exchange: Targeted Therapy for Thrombotic Thrombocytopenic Purpura

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Pharmacy Grand Rounds
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Objectives

- Describe the pathophysiology of thrombotic thrombocytopenic purpura (TTP)
- Review the current management of TTP
- Analyze literature supporting new targets for the treatment of TTP
Thrombotic Microangiopathy Syndromes

- TMA Syndromes
  - Thrombocytopenia
  - Organ injury
  - Microangiopathic hemolytic anemia
  - Arteriolar and capillary thrombosis

# Thrombotic Microangiopathy Syndromes

<table>
<thead>
<tr>
<th>Hereditary disorders</th>
<th>Acquired disorders</th>
</tr>
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<tbody>
<tr>
<td>ADAMTS13 deficiency-mediated TMA (TTP)</td>
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<td>(Upshaw-Schulman syndrome)</td>
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<td>Drug-mediated TMA (toxic dose-related reaction)</td>
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</tbody>
</table>

TMA: Thrombotic microangiopathy  
TTP: Thrombotic thrombocytopenic purpura  
HUS: Hemolytic uremic syndrome  

Acquired TTP

- Incidence is 4-11 cases per 1 million per year
- Increased association
  - Female sex
  - Black race
  - Obesity
- Severe functional deficiency in ADAMTS13, VWF-cleaving serine metalloprotease
  - Autoantibody inhibition of ADAMTS13 activity

VWF: Von Willebrand factor

Pathophysiology
Diagnosis

**Pentad of Clinical Features**

- Neurologic abnormalities
- Renal abnormalities
- Fever
- Microangiopathic hemolytic anemia
- Thrombocytopenia
- ADAMTS13 activity < 10%

- Schistocytes
- Hemoglobin↓
- Haptoglobin↓
- LDH↑
- Platelets < 150,000/uL

LDH: lactate dehydrogenase


Question 1

• Which of the following findings support the diagnosis of TPP?
  • Schistocytes
  • Thrombocytopenia
  • DVT/PE
  • A and B
  • All of the above
Treatment for Acquired TTP

**First line:** plasma exchange/steroids

**Refractory:** rituximab

**Salvage:** splenectomy, cyclosporine, cyclophosphamide/vincristine

**New agents:** caplacizumab, bortezomib

Plasma Exchange (PLEX)

- First line for all patients with suspected TTP
- Canadian Apheresis Study (1991)
  - PLEX is superior to plasma infusion
  - Plasma: source of replacement ADAMTS13
  - Exchange: removes anti-ADAMTS13 autoantibodies
- Continue daily PLEX for 2 days after platelet normalization

Pharmacist Considerations with PLEX

- Medication removal
  - Low volume of distribution
  - High protein binding
- Schedule medications after PLEX
- ACE-inhibitors are contraindicated
  - Unopposed bradykinin

Kale-Pradhan PB et al. Pharmacotherapy. 1997;17(4):684-95
Steroids

- Immunosuppression may produce a more durable response
- High dose vs. standard dose steroids
  - No difference in response at day 9
    - 76.6% vs. 56.7%, p=0.17
  - Improved remission rates at day 23
    - 76.6% vs. 46.6%, p=0.03

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Refractory, unstable, neurologic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone 1 mg/kg/day</td>
<td>Methylprednisolone 1 g/day x 3 days</td>
</tr>
</tbody>
</table>

Goals of Therapy

- Platelet recovery
  - > $150 \times 10^9$/L
  - Refractory if no response after 4-7 days
- Prevention of relapse
  - Risk of relapse is 20-50%

Rituximab

- Monoclonal antibody targets the CD20 antigen on B lymphocytes
  - Suppresses production of the anti-ADAMTS13 antibody

Lim W et al. Blood. 2015;125(10):1526-31
<table>
<thead>
<tr>
<th>Initial Treatment</th>
<th>Refractory Episodes</th>
<th>Relapse Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>Froissart et al. 2012</td>
<td>Hie et al. 2014</td>
</tr>
<tr>
<td>Design</td>
<td>Prospective, open-label</td>
<td>Observational, cross-sectional</td>
</tr>
<tr>
<td>Intervention</td>
<td>RTX (n=40) vs. historical control (n=40)</td>
<td>RTX (n=21) vs. historical control (n=53)</td>
</tr>
<tr>
<td>Results</td>
<td>Remission rates • RTX: 93% • Control: 95%</td>
<td>Durable remission by day 35 (p&lt; 0.02) • RTX: 100% • Control: 58%</td>
</tr>
<tr>
<td></td>
<td>Relapse rates • RTX: 11% • Control: 55% • P= 0.0011</td>
<td>Relapse at 1 year • No difference between groups</td>
</tr>
</tbody>
</table>

RTX: rituximab

Limitations

• Observational studies matched with historical controls
• Steroid and other salvage therapy use not controlled
• Shorter follow up duration in treatment groups
• Rituximab produces B-cell depletion for 9-18 months

Lim W et al. Blood. 2015;125(10):1526-31
## Rituximab

<table>
<thead>
<tr>
<th>Category</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Treatment</strong></td>
<td>• <strong>Maybe</strong>&lt;br&gt;RTX may decrease time to remission and may delay relapse</td>
</tr>
<tr>
<td><strong>Refractory Episodes</strong></td>
<td>• <strong>Yes</strong>&lt;br&gt;RTX appears to be effective for patients unresponsive to PLEX/steroids</td>
</tr>
<tr>
<td><strong>Prevention of Relapse</strong></td>
<td>• <strong>No</strong>&lt;br&gt;Benefit does not appear to outweigh risks and more evidence is needed</td>
</tr>
</tbody>
</table>

Caplacizumab

- Anti-VWF single-variable domain immunoglobulin
  - Targets the A1 domain of VWF
  - Prevents interaction with platelet receptor

# Caplacizumab for Acquired TTP

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate caplacizumab for treatment of acquired TTP</th>
</tr>
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<tbody>
<tr>
<td>Design</td>
<td>Phase II, randomized, controlled trial</td>
</tr>
<tr>
<td>Intervention</td>
<td>Caplacizumab 10 mg SC daily (n=36) vs. placebo (n=39) during PLEX and 30 days afterward PLUS standard of care</td>
</tr>
<tr>
<td>Results</td>
<td>Median time to a response</td>
</tr>
<tr>
<td></td>
<td>• Caplicizumab: 3.0 days (95% CI 2.7-3.9)</td>
</tr>
<tr>
<td></td>
<td>• Placebo:4.9 days (95% CI 3.2-6.6)</td>
</tr>
<tr>
<td></td>
<td>• Event rate ratio 2.20 (95% CI, 1.28-3.78, p = 0.005)</td>
</tr>
<tr>
<td></td>
<td>Exacerbations</td>
</tr>
<tr>
<td></td>
<td>• Caplicizumab: 8%</td>
</tr>
<tr>
<td></td>
<td>• Placebo: 28%</td>
</tr>
<tr>
<td></td>
<td>Relapses</td>
</tr>
<tr>
<td></td>
<td>• Caplicizumab: 22%</td>
</tr>
<tr>
<td></td>
<td>• Placebo: 0%</td>
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Conclusion and Role in Therapy

- Resulted in a more rapid resolution of TTP episodes
- May be effective for initial or refractory TTP
- Not effective for preventing relapse
- Not available outside of clinical trials

Bortezomib

- Proteasome inhibitor
  - Apoptosis of autoreactive plasma and B cells
  - Rituximab targets CD20+ B cells only
- Case reports and series (n=12)
  - Survival and clinical remission in 11/12 cases
- Place in therapy
  - Refractory TTP after lack of response to PLEX/steroids and rituximab

Question 2

• What is the recommended agent for patients with TTP who do not have a response to PLEX/steroids after 4-7 days?
  • Caplacizumab
  • Bortezomib
  • Rituximab
  • Eculizumab
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TMA: Thrombotic microangiopathy  
TTP: Thrombotic thrombocytopenic purpura  
HUS: Hemolytic uremic syndrome  
Hemolytic Uremic Syndrome (HUS)

Typical HUS (90%)

• Shiga-toxin producing *E. coli* (STEC-HUS)
  • Serotypes 0157:H7 and 0104:H4

Atypical HUS (10%)

• Genetic and acquired
• Uncontrolled complement activation

Diagnosis

- **Thrombocytopenia**
  - Platelet < 150,000/uL or 25% reduction from baseline

- **Microangiopathic hemolytic anemia**
  - Hemoglobin < 10 g/dL, schistocytes, decreased haptoglobin, increased LDH

- **Organ injury**
  - Kidney, CNS, GI tract

- **Exclusion of other TMA**
  - ADAMTS13 >5%
  - Toxin-producing bacteria negative

LDH: lactate dehydrogenase
CNS: central nervous system
GI: gastrointestinal

Clinical Consequences

- Lifelong risk of systemic thrombotic microangiopathy
  - Organ damage to kidneys, CNS, GI tract
  - 50% develop ESRD
- Poor prognosis
  - 25% mortality
  - High recurrence rate after transplantation (60-90% graft failure)

ESRD: end-stage renal disease

Treatment of Atypical HUS

First line: plasma infusion or exchange

New agent: eculizumab

Eculizumab

- Complement over-activation $\rightarrow$ atypical HUS
- Eculizumab binds to C5 complement protein and blocks production of MAC


MAC: membrane attack complex
# Eculizumab for Atypical HUS

<table>
<thead>
<tr>
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<th>Trial 1</th>
<th>Trial 2</th>
</tr>
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<tr>
<td><strong>Objective</strong></td>
<td>Evaluate safety and efficacy of eculizumab for atypical HUS</td>
<td></td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>AHUS and progressing TMA after $\geq 4$ PLEX/PI (n=17)</td>
<td>AHUS and long disease duration, CKD, prolonged PLEX/PI treatment (n=20)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Eculizumab IV 900 mg weekly x 4 weeks, then 1200 mg every 2 weeks x 26 weeks</td>
<td></td>
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## Results

<table>
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<tr>
<th>End point (at week 26)</th>
<th>Trial 1 (n=17)</th>
<th>Trial 2 (n=20)</th>
</tr>
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<tbody>
<tr>
<td>Change in platelet count from baseline, x10^9/L</td>
<td>73*</td>
<td>5</td>
</tr>
<tr>
<td>Thrombotic microangiopathy event-free status, %</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>Normalization of hematologic values, %</td>
<td>76</td>
<td>90</td>
</tr>
</tbody>
</table>

*N Engl J Med. 2016;368(23):2169-81*

*P* = <0.001
## Results

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<th>Trial 1 (n=17)</th>
<th>Trial 2 (n=20)</th>
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<tr>
<td>Increase in eGFR from baseline to week 26</td>
<td>32 mL/min/1.73 m² 95% CI 14-49, p=0.001</td>
<td>6 mL/min/1.73 m² 95% CI 3-9, p&lt;0.001</td>
</tr>
<tr>
<td>Increase in eGFR from baseline to week 60</td>
<td>32 mL/min/1.73 m² 95% CI 16-47, p&lt;0.001</td>
<td>9 mL/min/1.73 m² 95% CI 4-14, p=0.003</td>
</tr>
<tr>
<td>Discontinued dialysis</td>
<td>4/5 (80%)</td>
<td></td>
</tr>
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Conclusion

- Inhibited complement-mediated TMA
  - Platelet count recovery (Trial 1)
  - Absence of TMA events (Trial 2)
- Improved renal function
- Eculizumab should be started without results of complement mutation testing

Eculizumab Clinical Pearls

• REMS program
  • Increased risk of meningococcal sepsis

• Meningococcal vaccination
  • At least 14 days prior to dose OR
  • Vaccination plus antimicrobial prophylaxis for 14 days

Question 3

• In the Phase 2 trial, eculizumab demonstrated which of the following outcomes?
  • Platelet count recovery
  • Prevention of TMA events
  • Improvement in GFR
  • All of the above
## Summary

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<tr>
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<th>Acquired TTP</th>
<th>Atypical HUS</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MAHA</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>ADAMTS13 &lt;10%</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>PLEX</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Steroids</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Rituximab, caplacizumab, bortezomib</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Eculizumab</td>
<td></td>
<td>✓</td>
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MAHA: microangiopathic hemolytic anemia
Future Directions

• Acquired TTP
  • Role of caplacizumab and bortezomib
  • Optimal dose, timing, and sequence of therapies
  • Agents for prevention of relapse

• Atypical HUS
  • Optimal duration of eculizumab therapy
  • Treatment of refractory patients

Conclusion

• Acquired TTP is caused by autoantibody inhibition of ADAMTS13 activity

• PLEX and steroids are recommended for first line treatment

• Several new agents targeted at the underlying mechanism have shown efficacy
Questions & Discussion