The Treatment of TTP and the Prevention of Relapses

GERALD APPEL, MD
Professor of Clinical Medicine
Columbia University – College of Physicians and Surgeons
NY-Presbyterian Hospital
New York, New York
Thrombotic Thrombocytopenic Purpura

• A 36 AA year old previously healthy female has a baseline BUN of 10 mg/dl and a serum creatinine of .07 mg/dl.
• She develops fever and bruising.
• She goes to her LMD and examination shows ecchymoses on legs and arms.
• CBC shows wbc 10.2K, plats 15 K, Hct 28%, LDH 1,825
• PT and PTT are normal.
Thrombotic Thrombocytopenic Purpura

microangiopathic hemolytic anemia.

Over the next day her urine output declines and she develops decreased vision followed by decreased mental status. BUN is 32 mg/dl, creatinine 1.6 mg/dl.
Thrombotic Thrombocytopenic Purpura

• Do we wait for an ADAMTS13 level to treat?
• What initial therapy is best? Plasma infusion? Plasma exchange?
• Should Glucocorticoids be used?
• When should Rituxan be used? Cyclosporine, vincrisitne, IVIG???
• What is the chance of her relapsing? What therapy then?
The Treatment of TTP

• What is the standard treatment of TTP?
• What is the risk of not treating?
• What to do about atypical cases or before the dx is confirmed?
• Who relapses and how to prevent this?
The Diagnosis of TTP in Adults

- Clinical Features of neurologic abnormalities and acute renal failure
- Thrombocytopenia and Microangiopathic hemolytic anemia without another cause
- Histologic evidence of thrombotic microangiopathy
- Effective deficiency of von Willebrand factor-cleaving protease (ADAMTS-13)
Von Willebrand Factor

[Diagram showing the structure of Von Willebrand Factor (VWF) with labeled domains and interactions.]
Figure 2 Pathogenesis of idiopathic TTP caused by ADAMTS13 deficiency

Sadler, J. E. Blood 2008;112:11-18
Pregnancy

Drug association

Malignancy

Autoimmune (severe SLE)

Stem Cell Transplant

Systemic Sclerosis

Malignant HTN

HIV 0.3%

TTP
Relation of ADAMTS13 activity to clinical categories of 142 patients with clinically diagnosed TTP-HUS


<table>
<thead>
<tr>
<th>ADAMTS13 Activity</th>
<th>&lt;5%</th>
<th>5-9%</th>
<th>10-25</th>
<th>&gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem cell transplantation (7)</td>
<td>0</td>
<td>0</td>
<td>1 (14)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Pregnant/postpartum (10)</td>
<td>2 (20)</td>
<td>0</td>
<td>0</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Drug associated (21)</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
<td>20 (95)</td>
</tr>
<tr>
<td>Bloody diarrhea (10)</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Additional/alternative disorders (46)</td>
<td>0</td>
<td>2 (4)</td>
<td>10 (22)</td>
<td>34 (74)</td>
</tr>
<tr>
<td>Idiopathic (48)</td>
<td>33%</td>
<td>8%</td>
<td>23%</td>
<td>36%</td>
</tr>
</tbody>
</table>
Oklahoma TTP-HUS Registry (1989-2007)

• All 382 consecutive pts for whom the Oklahoma Blood Institute was requested to provide plasma exchange for Dx of TTP or HUS

• Among patients with ADAMTS13 activity <5%
  – Median age 40
  – Black/Non-Black 9.3
  – Women/Men 2.7

• Incidence 3-10 per 10^6

• The incidence of non-idiopathic TTP much higher - difficult to determine (e.g. ~ 5% of pts with disseminated malignancy?)

George JN Kidney Int 2009; 75: S8-S10
Relation of ADAMTS13 activity to presentation in 142 pts with clinically diagnosed TTP-HUS

Presenting clinical and laboratory features

<table>
<thead>
<tr>
<th></th>
<th>ADAMTS 13 Activity</th>
<th>&lt;5%</th>
<th>5-9</th>
<th>10-25</th>
<th>&gt;25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe neuro abnormalities, %</td>
<td>44</td>
<td>43</td>
<td>74</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure   %</td>
<td>6</td>
<td>14</td>
<td>30</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Median platelet count, x 10⁹/L</td>
<td>11</td>
<td>7</td>
<td>12</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Median hematocrit, %</td>
<td>21</td>
<td>24</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>
The Risk of Not Treating

• Untreated TTP in adults typically is progressive with irreversible renal failure and neurologic deterioration.
• The mortality rate prior to the use of Plasma Exchange was 90%.
• With plasma exchange mortality reduced to as low as <10%-15%.
• Thus, even if Dx is uncertain – safest to institute therapy and D/C if another dx confirmed (e.g. disseminated infection, malignancy, etc.)
Rationale for Plasma Exchange Therapy in TTP

A deficiency of, or an autoantibody directed against, the von Willebrand factor cleaving protease (ADAMTS13) is responsible for most adult idiopathic TTP. The accumulation of large VWF multimers leads to platelet aggregation and platelet rich thrombi in tissues.

Plasma Exchange
1) Removes circulating autoantibodies to ADAMTS13
2) Removes circulating very high molecular weight VWF multimers
3) Replaces the missing protease ADAMTS13.
Plasma Exchange for TTP

• 108 TTP pts treated (All neg 0157:H7),
• 200 mg Pred/day for pts with minimal sxns and no CNS findings.
• Pred + PLEX for pts with rapid deterioration, rapid decline in HCT or platelet count, CNS disease, failure post 48 hrs pred alone.
• 91% survival.
• Pred alone effective in 30 pts (2 relapses and 2 deaths)
• PLEX + Pred in 78 pts (67 relapses and 8 deaths)
• Splenectomy, ASA, dipyridamole no help in those with poor response to PLEX.

Plasma Infusion for TTP
Plasma Exchange vs Plasma Infusion

• Prospective randomized trial of PLEX vs Plasma infusion in TTP by Canadian Apheresis Study Group.
• 102 Pts get PLEX or Plasma Infusion on 7 of 9 days after entry (total volume of plasma received with PLEX 3x that of PI. All got ASA and dipyridamole)
• Compared at day 9 and 6 months w response defined by an increase platelet count.

Plasma Exchange vs Plasma Infusion

At the end of the first 9 days:
- PLEX 47% responded vs 25% with PI (p=.025)
- PLEX 4% deaths vs 16% deaths PI.

After 6 months Rx:
- PLEX 78% responded vs 49% PI (p=.002)
- PLEX 22% died vs 37% PI died (p=.036).
- Overall mortality 29%
- Conclusion PLEX is more effective.
  (BUT more plasma given!)

• A review of randomized controlled trials on PLEX. 7 trials were identified as of 2005.
  – 2 studies compared PLEX to plasma infusion (total 140 patients). PLEX was associated with a statistical reduction in mortality vs. plasma infusion (RR 0.31, 95% CI 0.12-0.79).
  – 5 studies compared different replacement fluids:
    • 2 studies compared a solvent/detergent-treated plasma to FFP (N= 43 patients),
    • 3 studies compared a cryopoor or cryosupernatant to FFP (N= 97 patients).
    • No statistical difference in mortality with different replacement fluids.
TTP therapy: Plasma Exchange

- Daily PLEX (1–1.5 plasma volume with fresh frozen plasma or cryo-poor plasma).

- PLEX is continued until the platelet count (>150K) and hemolysis markers normalize.

- ~20% of patients show a minimal or transient response to initial PLEX. Subsequent treatment may include increasing PLEX to twice daily (with cryo-poor plasma), or the addition of prednisone, vincristine or IVIgG or Rituximab.

- Splenectomy may be considered
- Additional immunosuppressive agents (cyclosporine) may be of benefit

*Kidney International (2009) 75 (Suppl 112), S55–S58*
Plasma Exchange – Complications

- Complications of PLEX for TTP in 11 Hosps over 3 yrs. (major 30% and minor 31%)
- 27 Major with 2 deaths in 21 pts.
- 2 reaction to PLEX and one serum sickness.
- 24 related to central catheter – (10 bacteremia with 1 death, 2 hemorrhage with 1 death, 2 fungemia 2 DVT, 1 pneumothorax)
- 22 Minor reactions (urticaria, hypotension, catheter obstruction, local catheter infections, bleeding at exit site.)

- Long-term experience in 12 years in 249 consecutive pts and 2924 procedures – 83 major complications with 7 deaths. (deaths related to catheter placement or sepsis.)

What does not work in TTP

- **Antiplatelet therapy** (ASA, dipyridamole) alone - (? Role with PLEX. Do not use in those w plats < 50K.)
- **Platelet transfusions** – may worsen CNS or cause ARF. (could not show a detrimental effect in one registry – ???may be used in prep for invasive procedures)
- **Splenectomy** of no benefit unless accompanied by PLEX and steroids.
Role of Glucocorticoids in TTP

- Often levels of ADAMTS13 not available at presentation.
- If idiopathic TTP (no drug induced, no bloody diarrhea, no stem cell txp, no malignancy, etc.) and poor response to initial therapy with PLEX can add prednisone 1mg/kg day PO or methyl pred 125 mg BID
- Use in pts whose plt counts do not increase w/i several days of PLEX or whose thrombocytopenia recurs as PLEX decreased.
- or JUST ADD STEROIDS FROM START.
PLEX + Rituximab

• 15 patients with TTP, 8 received Rituximab.
• The overall response rate to rituximab plus plasma exchange was 100%, compared to 65.8% for plasma exchange alone.
• Median progression free survival with rituximab was 3.8 years, vs. 0.1 years in the standard-treatment group.

PLEX + Rituximab: Pooled analysis

- Total N=42
- Course of rituximab varied greatly (1 – 13 weekly doses at 375 mg/m2) - 4 doses most common.
- Complete remission rate of 90%
- Median response duration: 23.5 months (range 13–79).
- Relapses in 21% of pts after 13 to 46 months with no early relapses.
- Although rarely reported, depletion of circulating CD20+ B cells was confirmed despite the concurrent use of PLEX.
- A systematic review of adverse events was not performed.
Evaluating the Addition of Rituximab to Standard Treatment of TTP - STAR

- **Sponsors:** NHLBI and Genentech
- **RCT 238 patients with do novo or relapsing TTP**
- **Experimental group:** rituximab in addition to PLEX and corticosteroids
  - Rituximab: 375 mg/m² IV q week x4
  - Daily PLEX of 1.25 plasma volume with FFP replacement until platelet count are normal and signs of tissue damage have improved.
  - Prednisone 1 mg/kg/d until PLEX is stopped, the tapered over 7 weeks
- **Active comparator:** PLEX and corticosteroids
- **Follow up:** 3 years  Expected completion 2016

*Clinicaltrials.gov: NCT00799773*
Other Agents for TTP

- **Cyclosporine** - rarely used since it produces a TTP-like picture of its own.
- 12 pts in literature who were resistant or had treatment failures with PLEX +/- Pred. With good responses.
- May have some effect, but only use in TTP pts without a remission with PLEX and steroids and currently more experience with rituximab.
- **IVIG** – mechanism unclear, clearly not a first-line therapy.
- **Vincristine** - limited data.

## Relation of ADAMTS13 activity to Outcome in 142 patients

<table>
<thead>
<tr>
<th>ADAMTS13 Activity</th>
<th>&lt;5%</th>
<th>5-9%</th>
<th>10-25</th>
<th>&gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, % (proportion)</td>
<td>89 (16/18)</td>
<td>71 (5/7)</td>
<td>39 (9/23)</td>
<td>60 (56/94)</td>
</tr>
<tr>
<td>Exacerbation, %</td>
<td>56</td>
<td>80</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>Median no. of plasma exchange</td>
<td>21</td>
<td>45</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>TTP-HUS-associated death, % (proportion)</td>
<td>17</td>
<td>14</td>
<td>61</td>
<td>35</td>
</tr>
<tr>
<td>All death, % (proportion)</td>
<td>17</td>
<td>29</td>
<td>70</td>
<td>53</td>
</tr>
<tr>
<td>Relapse rate</td>
<td>44</td>
<td>17</td>
<td>11</td>
<td>33</td>
</tr>
</tbody>
</table>
Follow of Relapsing Disease

- Relapses defined as recurrent TTP after 30 days of no TTP findings and no treatment.
- Usually recur in first yr but up to 10 yrs!
- Can Apheresis Study – 63 pts followed 3-10 yrs relapse rate 36%.
- Morbidity and Mortality less for relapses than initial episode (less delay in Dx and pts who respond to PLEX usually respond again).
- For repeat relapses – rituximab, Cyclosporine, Splenx, etc.
Prognostic value of ADAMTS 13

- Prospective study of 35 adults with first episode of TMA, <5% ADAMTS13 activity,
- All treated with corticosteroids and PLEX.
- Remissions in 32 pts (91.4%) - 3 pts died.
- At presentation, ADAMTS13 antigen decreased in >91%, and ADAMTS13 inhibitor detectable in 89%.
- Among survivors, ADAMTS13 activity in remission increased to > 15% in 59%, but was undetectable in 41%.
- High levels of inhibitory anti-ADAMTS13 IgG at presentation were associated with the persistence of an undetectable ADAMTS13 activity in remission, the latter being predictive for subsequent relapses.

Outcome of Treated TTP

- Residual CNS disease – cognitive.
- Other organ Damage.
- Renal disease in approximately ¼ pts (especially pts with initial ADAMTS13 >10%).

Structure of ADAMTS13

Sadler, J. E.  Blood 2008;112:11-18