Thrombotic Thrombocytopenic Purpura (TTP) an update

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April 2019
Thrombotic Thrombocytopenic Purpura (TTP) an update

Focus:
New treatments
Improvement in patients outcome
Thrombotic Thrombocytopenic Purpura

- An Hematological emergency
- **High mortality rate**:  
  Without treatment 90%  
  With treatment 10-20%

- **Long term sequela**:  
  Up to 50% of patients will experience relapse  
  Neurological impairment, cognitive deficits  
  Hypertension  
  Depression  
  Headaches  
  Increased incidence of stroke?
TTP clinical presentation

- Microangiopathic hemolytic anemia (MAHA)
- Thrombocytopenia
- Organ failure of variable severity:
  - neurological (65%), renal (47%), heart, gastrointestinal
- Fever (20%)

- Classical pentad 5-40% of patients

Diagnosis can be delayed: non specific complains “flu like”

- Weakness (60%) myalgia, arthralgia
- GI symptoms (70%)
- Bleeding tendency (54%)
- SOB (30%)
- Chest pain (20%)
TTP pathogenesis

Deficiency/inhibition of ADAMTS13 microvascular platelet rich thrombi
TTP diagnosis

- Severe ADAMTS13 deficiency activity < 10%

**Congenital**
(Upshaw-Schulman syndrome)
~ 5% of all primary TTP forms
More than 100 diff mutations
Chronic relapsing disease
Childhood
Women of childbearing age

**Immune-mediated**
Idiopathic
Antibodies to ADAMTS13
3.7/106/year
75% women
Age 40-60y
black

**TTP like ADAMTS >10%**
HUS
Malignancy
BMT
Drugs
HIV
Lupus, RA
HELLP
TTP diagnosis

Known underlying or associated condition
- STX-HUS
- Drug-associated TMA
- Transplantation-associated TMA
- Cancer
- HIV infection
- Pregnancy

• Platelet count
• Creatinine level

<30\times10^9 \text{ cells per litre}
<2.25 \text{ mg per dl}

TTP suspected

≥30\times10^9 \text{ cells per litre}
≥2.25 \text{ mg per dl}

Atypical HUS suspected

≥10%

Consider
- HUS
- Other TMA

ADAMTS13 activity

<10%

TTP confirmed

Antti-ADAMTS13 IgG assay

Positive

Immune-mediated TTP

Negative

ADAMTS13 activity and anti-ADAMTS13 IgG persistently undetectable during remission

No

ADAMTS13 gene analysis

Yes

Congenital TTP

Kremer Hovinga JA et al
Nat Rev Dis Primers, 2017
TTP treatment

Classical treatment:
• Plasma Exchange (PEX) as soon as TTP suspected
• Steroids
• Folic acid
• Platelets (uncertain evidence of harm Swisher et al Transfusion 2009)
• Consider aspirin after increase in platelet count

Refractory disease: (10-42%)
Failure of platelet response after 4 to 7 days of PEX.
Clinical deterioration in a patient receiving standard therapy.
In addition: 30% of patients will relapse soon (30d) after stopping PEX
TTP treatment Cont.

New treatments:
• Rituximab
• Caplacizumab
• N-acetyl cysteine – mucomyst
• Bortezomib

Other options:
• Cyclosporine, Vincristine, Cyclophosphamide
• Splenectomy
Plasma Exchange (PEX)

# Daily PEX is the current mainstay of treatment and has reduced mortality from over 90% to 10-20%.

# Removal of antibodies and repletion of ADAMTS 13.

# Stopped when PLT are above 150K for at least 2 consecutive days.

# PEX has been shown to be superior to plasma infusion at the end of first treatment cycle and at 6 month (78% vs. 49%)
also improved survival (Rock NEJM 1991; 325: 393-7)
All patients received aspirin 325mg and dipyridamole

(Rock NEJM 1991; 325: 393-7)
Steroid treatment in TTP

# Autoimmune disease.

# There are no randomized controlled trial addressing whether a combination of PEX and corticosteroids is superior to PEX alone.

# Type and dose of steroids – unknown.

# One RCT including 60 patients that showed that higher doses of methylprednisolone CR ↑ (53% vs 23% after 23 days)
10mg/kg/d for 3 days followed by 2.5 mg/kg/d for 23 days versus 1 mg/kg/d

(Balduini, annals of hematology 2010; 89:591-596)

British guidelines: Scully et al 2012
Give steroids; either IV methylprednisolone (1 g/day for 3 days) or oral prednisolone (e.g. 1mg/kg/day) with an oral proton pump inhibitor
Rituximab treatment in TTP

1. Suboptimal response to PEX
   - Improved platelet recovery median of 11 to 14 days after the first dose.
   - Clinical remission - 87% to 98% of patients. (retrospective + prospective)

2. Initial treatment
   - Shorter hospitalization
   - Fewer relapses (11% v 55%)
   - Remission >90%
   - However, may expose patients to overtreatment
   - Low dose?

Joly BS et al Blood 2016
Masias C et al RPTH 2017
Low dose rituximab for initial treatment?  
ART study

Rationale:

• Dosing of 375 mg/m2 established for lymphoproliferative disorders
• B cell mass is less in non-malignant conditions
• Lower cost
• Evidence to support low dose rituximab in ITP
• Prospective phase II single arm study
• Rituximab 100 mg X4 in addition to PEX + steroids
• Primary outcome – incidence of exacerbation in 30d or refractory disease-failure to achieve treatment response by day 28 or durable response at day 60

Zwicker JI et al, Beth Israel, Harvard medical school, ASH 2018 paper no 374
Low dose rituximab for initial treatment? ART study

• 18 patients
• 2 exacerbations (achieved durable responses at 29 and 35 days)
• No cases of refractory disease
• B cell depletion in 12 months – similar to 375mg regimen
• Primary end point – 12% in 30 days (compared to 48% in historical controls w/o rituximab)
• 28% relapse in 2 years (compared to 51% in historical controls)

**Conclusion:** Low dose rituximab decreases incidence of exacerbations and refractory disease.
A direct comparison should be made to 375mg regimen

Zwicker JI et al, Beth Israel, Harvard medical school, ASH 2018 paper no 374
Rituximab treatment in TTP

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   - Shorter hospitalization
   - Fewer relapses (11% vs 55%)
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   - However, may expose patients to overtreatment
   - Low dose?

3. Prophylaxis
   - Preemptive for patients with ADAMTS activity <10%

Joly BS et al Blood 2016
Masias C et al RPTH 2017
C. Preemptive Rituximab treatment in TTP

Up to 50% of patients will experience relapse
Persistently undetectable ADAMTs activity <10% predicts relapse:
38% after 1 year
59% after 5 years

Preemptive infusion of rituximab in patients with undetectable ADAMTs activity → rapid recovery of ADAMTs in most patients, however recovery may not sustain
Preemptive Rituximab prevents long term relapses in immune mediated TTP

- Patients with idiopathic TTP
- Treated with PEX+ steroids
- Rituximab for refractory or exacerbation
- ADAMTs13 levels tested after acute phase and every 3 months
- **Patients with ADAMTs activity <10% received rituximab**
- Patients who responded and reduce ADAMTS levels – **retreatment** with rituximab
- Follow up – at least 12 months

- Patients received 1(n=42), 2 (n=15) 4 (n=33) , 5 (n=1) doses of rituximab
- Mostly 375mg m2 (n=79) but also 500mg m2(n=13)

Jestin M et al Blood 2018;132(20)2143-2153
Frence reference center for thrombotic microangiopaties
Patients with a history of iTTP who received a first course of preemptive rituximab (ADAMTS13 activity < 10% during follow-up)

116

- Missing data (5) or follow-up < 1 year (19)
- Persistent severe ADAMTS13 deficiency (13)

Patients available for analysis
92

- ADAMTS13 recovery (79)

Sustained ADAMTS13 recovery (34)

- Clinical relapse
  - Did not follow appropriate ADAMTS13 assessment: 4
  - Relapse before preemptive rituximab could be administered: 1

Recurrence of severe ADAMTS13 deficiency (45)

- Retreatment(s) (38)
  - Clinical relapse: 1
  - No treatment: 1 (no clinical relapse)

- No further preemptive rituximab (clinician’s decision) (2)
  - Clinical relapse: 1
  - No treatment: 1 (no clinical relapse)

ADAMTS13 recovery; no clinical relapse (31)

- Failure to recover ADAMTS13 activity: 3
  - Relapse before preemptive rituximab could be administered: 3 (1 fatal)
  - Unsustained response with loss of responsiveness: 1

Cyclosporine A: 2 (recovered)

No treatment: 1 (no clinical relapse)
B

Persistent severe ADAMTS13 deficiency 13

Repeated rituximab administration 10

No treatment: 1 (no clinical relapse)
  Cyclosporine A: 1 (recovered)
  Cyclosporine A + bortezomib: 1*

ADAMTS13 recovery 6

Fatal clinical relapse 1

Persistent severe ADAMTS13 deficiency 4

No additional treatment: 3\textsuperscript{f}
  Cyclosporine A: 1 (recovered)

Clinical relapse 2

Clinical relapse 1
  Unsustained response with secondary refractoriness

\textsuperscript{f} Fatal clinical relapse 1
60%
Preemptive rituximab in patients with severe ADAMTS13 activity?

Decrease TTP relapse in 85% of patients

Median of 0.33 relapse episodes/year IQR (0.23-0.66) to a median of 0 episodes/year (IQR 0-1.32)

Jestin M et al Blood 2018;132(20)2143-2153
Caplacizumab (Cablivi) in aTTP

A vWF targeting Nanobody

Caplacizumab’s mode of action blocks binding of vWF to platelets which has an immediate effect on platelet adhesion and the ensuing microthrombi formation.
Nanobodies: derived from heavy chain only antibodies

- *Camelid* heavy-chain only antibodies are stable and fully functional

**Ablynx’s Nanobody**
- small and robust
- easily linked together
- sequence homology comparable to humanised/human mAbs
- nano- to picomolar affinities
- able to bind and block challenging targets
- multiple administration routes
- manufactured in microbial cells
**Phase II TITAN study**¹

Single-blind, randomized, multicenter placebo-controlled trial

75 patients recruited
- 36 caplacizumab arm
- 39 placebo
- 32 active sites

n=108 patients received caplacizumab


**Phase III HERCULES study**²

Double-blind, randomized, parallel group, multicenter placebo-controlled trial

145 patients recruited
- 72 caplacizumab arm
- 73 placebo
- 55 active sites

TITAN (phase II) - Study design

Results:
Faster resolution of TTP
Decreased Relapse rate during treatment (n=3 versus n=11)
More relapses after stopping caplacizumab (22%)

- PE, plasma exchange; FU, follow-up; s.c., subcutaneous; aTTP, acquired thrombotic thrombocytopenic purpura.
HERCULES (phase III) - Study design

- PE, plasma exchange; TTP, thrombotic thrombocytopenic purpura.
Hercules: Concomitant immunosuppression

Corticosteroids and Rituximab

<table>
<thead>
<tr>
<th>Immunosuppressive therapies</th>
<th>Caplacizumab N=72</th>
<th>Placebo N=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily PEX period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>68 (95.8%)</td>
<td>71 (97.3%)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>12 (17.1%)</td>
<td>21 (28.8%)</td>
</tr>
<tr>
<td>Post-daily PEX period</td>
<td>N=65</td>
<td>N=64</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>55 (84.6%)</td>
<td>60 (93.8%)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>22 (33.8%)</td>
<td>23 (35.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of corticosteroid/cumulative dose (overall treatment period)</th>
<th>Caplacizumab N=72</th>
<th>Placebo N=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration of corticosteroid use (days)</td>
<td>30.5</td>
<td>31.3</td>
</tr>
<tr>
<td>Cumulative dose of corticosteroids (mg)</td>
<td>2398.34</td>
<td>2352.27</td>
</tr>
</tbody>
</table>

PE, plasma exchange.

Hercules Primary endpoint: time to platelet count response*

Percentage of patients without platelet count normalization

<table>
<thead>
<tr>
<th>Time (days) since first dose of study drug</th>
<th>Caplacizumab N=72</th>
<th>Placebo N=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>78.2%</td>
<td>56.8%</td>
</tr>
<tr>
<td>Day 4</td>
<td>88.4%</td>
<td>74.1%</td>
</tr>
<tr>
<td>Day 5</td>
<td>94.2%</td>
<td>77.1%</td>
</tr>
</tbody>
</table>

Platelet normalization rate ratio (95% CI) 1.55 (1.10, 2.20)

Stratified* log-rank test p-value <0.01

* Platelet count response was defined as initial platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days

CI, confidence interval; PE, plasma exchange; GCS, Glasgow coma scale.

Other secondary endpoints – HERCULES study\(^1\)

Plasma exchange parameters, duration of ICU stay and overall hospitalization

<table>
<thead>
<tr>
<th>Overall study drug treatment period (mean±SE)</th>
<th>Caplacizumab N=71</th>
<th>Placebo N=73</th>
<th>% relative reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days of PE</td>
<td>5.8±0.5</td>
<td>9.4±0.8</td>
<td>↓38%</td>
</tr>
<tr>
<td>Volume of plasma (L)</td>
<td>21.3±1.6</td>
<td>35.9±4.2</td>
<td>↓41%</td>
</tr>
<tr>
<td>Number of days in ICU</td>
<td>3.4±0.4 (n=28)</td>
<td>9.7±2.1 (n=27)</td>
<td>↓65%</td>
</tr>
<tr>
<td>Number of days in hospital</td>
<td>9.9±0.7</td>
<td>14.4±1.2</td>
<td>↓31%</td>
</tr>
</tbody>
</table>

Overall number of PE days during the treatment period (TITAN and HERCULES)\(^2\)

<table>
<thead>
<tr>
<th>Overall treatment period*</th>
<th>Caplacizumab N=108</th>
<th>Placebo N=112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of PE days</td>
<td>6.5</td>
<td>10.4</td>
</tr>
<tr>
<td>SD</td>
<td>4.53</td>
<td>7.74</td>
</tr>
<tr>
<td>median</td>
<td>5.0</td>
<td>7.5</td>
</tr>
</tbody>
</table>

PE, plasma exchange; ICU, intensive care unit; L, liter.
Time to normalization of organ damage markers

ULN, upper limit of normal.
Subjects with aTTP-related death, aTTP recurrence or a major thromboembolic event during the study drug treatment period

<table>
<thead>
<tr>
<th>Number of subjects (%)</th>
<th>Caplacizumab N=72*</th>
<th>Placebo N=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects with at least one of the events&lt;sup&gt;1&lt;/sup&gt;</td>
<td>9 (12.7)</td>
<td>36 (49.3)</td>
</tr>
<tr>
<td>aTTP-related death&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>recurrence of aTTP&lt;sup&gt;3&lt;/sup&gt; (exacerbation)</td>
<td>3 (4.2)</td>
<td>28 (38.4)</td>
</tr>
<tr>
<td>at least one treatment emergent major thromboembolic event&lt;sup&gt;2&lt;/sup&gt;:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cerebrovascular accident</td>
<td>2 (2.8)</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>- myocardial infarction</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>- pulmonary embolism</td>
<td>1 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>- deep venous thrombosis (spontaneous)</td>
<td>0</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>- deep venous thrombosis (catheter-associated)</td>
<td>3 (4.2)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* percentages are based on 71 subjects entering the study drug treatment period;
<sup>1</sup> patients could have more than 1 event;
<sup>2</sup> adjudication of aTTP-related death and major thromboembolic events by a blinded independent committee;
<sup>3</sup> recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PE

aTTP, acquired thrombotic thrombocytopenic purpura; PE, plasma exchange.

Open label: 2/71 versus 26/73 (placebo)
Mortality rate (TITAN +Hercules)

- Mortality rate during the treatment period

<table>
<thead>
<tr>
<th>Total number of subjects – n (%)</th>
<th>Caplacizumab N=108</th>
<th>Placebo N=112</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>NA</td>
<td>(1.0, 8.9)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0477</td>
<td></td>
</tr>
</tbody>
</table>

- Mortality during the follow-up period, after end of treatment
  - One subject in the placebo group died 2 days after withdrawal of study drug (by physician decision) due to very severe refractory TTP, and was not considered as a death during the treatment period
  - One subject in the caplacizumab group died due to cerebral ischemia, which started 6 days after completing study drug treatment

Peyvandi F, ASH 2018, poster abstract, 373
Caplacizumab: Side effects TITAN+Hercules

- The most frequently reported adverse reactions (>15%) were:
  - Epistaxis
  - Gingival bleeding
  - Headache

- Serious bleeding adverse reactions reported in ≥2% patients included epistaxis (4%) and subarachnoid hemorrhage (2%)

- Seven patients (7%) in the CABLIWI group experienced an adverse reaction leading to study drug discontinuation
  - None of the those adverse reactions were observed in more than 1% of patients.
Bortezomib in the treatment of refractory thrombotic thrombocytopenic purpura

Rationale: Patients who are refractory to PEX and steroids and rituximab may have plasma cells producing antibodies
Case reports/ small case series report good response
Largest series: 6 patients

Patriquin et al, British Journal of Haematology, Volume: 173: 779-785,
N-acetyl cysteine

# The rationale for NAC use in TTP: structural similarities between VWF and mucin, which are both polymers formed by intra- and inter-molecular disulfide bonds.

NAC: mucomyst – break disulfide bonds and loosen thick mucus

# Widely available.
# Cheap
# Safe

Can it also reduce size of ULvWF multimers?

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Case reports with mixing results in refractory patients
New development in TTP:

1. Caplacizumab
   a. faster resolution of platelet count decreases plasma exchange/ stay in ICU
   b. reduce relapse rate
   c. May reduce end organ damage
   d. may reduce mortality

2. Rituximab:
   a. initiate early for refractory or relapsed patients
   b. highly consider Rituximab for prevention of relapse in patients with reduced ADAMTS13

3. For refractory patients consider NAC / bortizomib
Thank You!