New insights in thrombotic microangiopathies: TTP and aHUS

Dr Catherine LAMBERT
Hematology
Cliniques universitaires Saint-Luc
Catherine.lambert@uclouvain.be
New insights in thrombotic microangiopathies (TMA)
Physiopathology of TMA

- **Pathologic lesion**: TMA of arterioles or capillaries. Intraluminal platelets and fibrin microthrombi, obstruction of the vessel and tissue ischemia

- **Biological markers**: thrombocytopenia and mechanical microangiopathic hemolytic anemia (schistocytosis)

- **Clinics**: variable degree of organ dysfunction (kidney, brain, heart, lungs and gastro-intestinal tract)
  - aHUS: predominant renal impairment
  - TTP: predominant neurological abnormalities +/- renal (not always)
Etiology of endothelial damage

TMA
TMA classification

**Thrombotic thrombocytopenic purpura (severe ADAMTS 13 deficiency (<5-10%))**

- Acquired or idiopathic: anti-ADAMTS 13 antibodies
- Hereditary: mutation in ADAMTS 13 gene (Upshaw-Shulman syndrome)

**Hemolytic uremic syndrome**

- Typical: Shiga toxin-producing E.Coli
- Atypical: Alternate complement pathway dysregulation
  - Congenital
  - Acquired (anti-CFH)

**Secondary TMA (can also have lower ADAMTS 13 activity)**

- Stem cell/solid organ transplant
- Pregnancy/HE LLP
- Malignant hypertension
- Drugs
- Cancer
- Infection/DIC/HIV
- Autoimmune disease (SLE, APLS)
- ...
Relation among the absence of ADAMTS 13 activity in vivo, excessive adhesion and aggregation platelets in thrombotic thrombocytopenic purpura.

Moake et al, NEJM 2002
Alternate pathway of complement and aHUS

Carla M. Nester and Christie P. Thomas, Blood 2012
Genetic defects in aHUS

Prognosis of aHUS Varies According to the Genetic Defect
Noris M et al, CJASN 2010

ESRD or Death

250 patients
Age at onset: birth to 83 years

Cumulative Event-Free Survival (%)

20
40
60
80
100
0
12
24
36
50
60
80
90
100
Months After Onset

ESRD or Death

50%
60%
67%
77%

MCP
Undetermined
CFI
C3
CFH

The majority of patients received some form of plasma therapy

<table>
<thead>
<tr>
<th>Gene or subgroup</th>
<th>Frequency</th>
<th>Risk of death or ESRD at 1yr</th>
<th>Risk of relapse</th>
<th>Recurrence after renal transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement factor H (CFH)</td>
<td>20-30%</td>
<td>50-70%</td>
<td>50%</td>
<td>75-90%</td>
</tr>
<tr>
<td>Membrane cofactor protein (MCP)</td>
<td>5-15%</td>
<td>0-6%</td>
<td>70-90%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Complement factor I (CFI)</td>
<td>4-10%</td>
<td>50%</td>
<td>10-30%</td>
<td>45-80%</td>
</tr>
<tr>
<td>Thrombomodulin (THBD)</td>
<td>3-5%</td>
<td>50%</td>
<td>30%</td>
<td>1 patient</td>
</tr>
<tr>
<td>C3</td>
<td>2-10%</td>
<td>60%</td>
<td>50%</td>
<td>40-70%</td>
</tr>
<tr>
<td>Complement factor B (CFB)</td>
<td>1-4%</td>
<td>50%</td>
<td>3/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Anti-CFH ab</td>
<td>6%</td>
<td>30-40%</td>
<td>40-60%</td>
<td>Yes if high titer</td>
</tr>
</tbody>
</table>
Therapeutic management of TMA

• Plasma exchange (PE) with FFP for restitution remains therapeutic cornerstone
• But
  – Complications related to the procedure/availability
  – Suboptimal responses (refractoriness/exacerbation) in 20%
  – Relapses: 20-40% of TTP
  – Irreversible organ damages (ESRD, ...)
  – Hematologic remission in 70-80% with PE but still mortality of 10-20%
Rituximab in TTP

- Rituximab decreases the production of anti-ADAMTS 13 antibody by depleting B cells and reduces excessive cytokine production in secondary TTP
- Higher remission rate were achieved
- Shorter time to remission in first line and in suboptimal response to PE
- Less relapses (increase of ADAMTS 13 activity)
- No acute or delayed side effects

**Compared to historical controls**

Froissart et al, Crit Care Med, 2012
De la Rubia et al, Transfusion and Apheresis Science, 2010
Caramazza et al, Blood transfusion 2010
Chemnitz et al, Ann Hematol 2010
Scully et al, Blood 2011
Remaining questions about rituximab in TTP
Inhibitors of VWF-platelet GPIb binding

• Prevention of the ULVWF- platelet aggregates and micro-thrombi by targeting the A1 domain of VWF

• GBR600 - ALX-0681 - ARC1779

• Efficient in prevention and treatment of early-stage TTP
• No effects on the causal anti-ADAMTS 13 antibody
• Reduced time to remission, limited number of PE and organ dysfunction
• Effects on recovery after organ damage remains to be determined
• Good safety (no bleedings )

Salles et al, Blood 2012
Callewaert et al, Blood 2012
Feys et al, Blood 2012
Cataland et al Am J of Hematol 2011
Preventive and therapeutic effects of ALX-0681 on biological markers of TMA

Callewaert et al, Blood 2012
Recombinant ADAMTS 13

- Animal model (ADAMTS 13 KO mice) mimicking TTP after administration of high dose rVWF
- Administration of rADAMTS 13 acts as prophylactic and therapeutic agent (by overcoming anti-ADAMTS 13 inhibitors)
- For patients with congenital ADAMTS 13 deficiency (in future)

Figure 1. Reversible thrombocytopenia in rVWF-challenged ADAMTS13 KO mice. Animals were administered 2000 VWF:RCo/Ukg BW of rVWF (●), and platelet counts were determined after 1, 3, and 14 days. A severe thrombocytopenia was noted on day 1 after the challenge. Thrombocytopenia persisted on day 3 but subsided by day 14 compared with untreated ADAMTS13 KO mice (○).

Figure 4. Prophylactic efficacy of rhADAMTS13. Before the challenge with 2000 VWF:RCo/Ukg BW of rVWF, one group of animals received 200 FRET5-U/kg BW rhADAMTS13 (rHA13-rVWF), whereas the control group received rVWF only (rVWF). Platelet counts were determined after 1 day. Whereas all animals of the control group developed severe thrombocytopenia (●), animals prophylactically treated with rhADAMTS13 (△) were protected.

Schiviz et al, Blood 2012
Gain-of-function ADAMTS 13 variants

- In acquired TTP, IgG bind the spacer domain of ADAMTS13 main functional for recognition and proteolysis of VWF.
- Variant ADAMTS 13 with a modified exosite in the spacer domain reduced antibody binding and preserved or enhanced cleaving activity.

Cui Jian et al, Blood 2012
N-acetylcysteine

- Inhibits the VWF polymerisation by reduction of disulfide bonds
- Removes ULVWF strings from the endothelial surface and protects the endothelium from apoptosis and shear stress injury
- Inhibits VWF-platelets aggregation and collagen binding
- In mice model, rapid resolution of thrombi and reduced plasma VWF multimers
- Safe and low cost

Chen et al, Journal of clinical investigation 2011
Eculizumab in aHUS

• Stops the TMA progress
• Studies in adults and children confirm tolerance
• **Potential indications:**
  – For salvage therapy in nonresponse to PE after 3-5 days (persistent thrombocytopenia/ongoing hemolysis/lack in renal function improvement)
  – Prevention for aHUS relapse
  – Preserve native kidney or graft (long term treatment)
  – PE dependance
  – First line in children in order to avoid PE or plasma infusions complications

• Posology in adults: 900 mg/w, w1-4; 1200 mg w5; then 1200mg every 2 w. STOP PE to avoid clearance

Loirat et al, Presse Medicale 2012
Zuber et al Nature Reviews Nephrology 2012
# Hematologic Normalization Was Achieved and Maintained Through 2 Years with Ongoing Eculizumab

<table>
<thead>
<tr>
<th>90 (68-99)</th>
<th>90 (68-99)</th>
<th>90 (68-99)</th>
</tr>
</thead>
</table>

**Hematologic normalization** = Normal platelet (=150×10⁹/L) and LDH levels, 2 consecutive measurements, 4 weeks apart

 Patients achieved and maintained hematologic normalization regardless of the identification of a genetic complement mutation¹

- 13/14 (93%) of patients with known complement mutation
- 5/6 (83%) of patients without known complement mutation

---

*Percentage and 95% CI; †median duration 62 weeks; ‡median duration 114 weeks.
Goodship T et al. Presented at ASN; November 1, 2012; San Diego, CA. Poster TH-PO442.
TT30: a selective inhibitor of the complement alternate pathway

• Fusion protein that would preferentially accumulate at sites undergoing complement-mediated attack.
  – minimize the systemic complement inhibition (infections, auto-immune disease)
  – lower the dose required for clinical benefit
  – increase the target tissue residency time of the inhibitor

• TT30 is a selective inhibitor of the complement alternative pathway with the capability to provide durable local tissue binding and protection from hemolysis with only minimal transient systemic inhibition.

Fridkis et al, Blood 2012
Conclusions

• Early recognition of TMA is crucial

• PE without delay remains the first line treatment

• Very exciting therapeutic development aiming to
  – Reduce thrombi and organ damage
  – Reduce PE numbers
  – Reduce relapses