Treatment of thrombotic thrombocytopenic purpura

What is new?

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Reference Center for Thrombotic Microangiopathies

American Society For Apheresis – May 2017
TTP pathophysiology

Large vWF multimers
(20000 kDa)

ADAMTS13 (50-150%)

ADAMTS13 <10%

Lower molecular weight multimers
(500 kDa)

Excessive platelet aggregation

Systemic microthrombi
MOF and death

Short(/long)-live Plasmocytes

VWF multimers
NHP
TTP
**Pathophysiological basis of TTP treatment**

1. **Replenish ADAMTS13 levels:**
   - Saturate anti-A13 Abs
   - Cleave large vWF multimers

2. **Immunomodulation**
   - Target specifically B-cells (rituximab)
   - Target T-cells (cyclosporine A)
   - Target plasma cells (bortezomib)
   - Other non specific immunosuppressors: steroids, CPM, VCR..., splX

3. **Inhibition of platelet-vWF interaction**
   - Inhibitors of vWF polymerization (NAC)
   - Inhibitors of vWF-gp1b axis

Very large volumes of plasma (TPE) (exogenous A13)
Standard treatment of TTP

Daily therapeutical plasma exchange (+ steroids) in emergency until remission = core treatment of TTP

With this regimen, prognosis was outstandingly improved

Clinical/hematologic remission is currently of 85%, vs almost 0% before
Unmet needs with standard treatment 1.

Exacerbations (~ 50% of patients)  

Refactoriness (~ 10% of patients)

Patients with a **suboptimal response** to standard treatment

Exposed to a higher risk of death  

TPE-related complications  

(28% of cases)

How to improve these results?

*CNR-MAT, Br J Haematol 2006; Howard et al., Transfusion 2006*
Rituximab as an immunomodulator: the second breakthrough

Scully et al., Br J Haematol 2006

Refractory TTP or exacerbation: 14 cases

<table>
<thead>
<tr>
<th>Cerebral/cardiac involvement</th>
<th>12/2</th>
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<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>6.8 (5.1-9.6)</td>
</tr>
<tr>
<td>Platelets (x10⁹/L)</td>
<td>13 (5-33)</td>
</tr>
<tr>
<td>LDH (UI/L)</td>
<td>1750 (679-2832)</td>
</tr>
<tr>
<td>ADAMTS13 activity</td>
<td>&lt; 5% (12/14)</td>
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<td></td>
<td>12% (1/14)</td>
</tr>
<tr>
<td>Inhibitor or anti-ADAMTS13 Abs</td>
<td>13/14</td>
</tr>
<tr>
<td>ADAMTS13 &gt; 4 rituximab</td>
<td>90% (29-109%)</td>
</tr>
<tr>
<td>Inhibitor/Abs &gt; 4 rituximab</td>
<td>0/↓ significative</td>
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Relapsing TTP: 11 cases

<table>
<thead>
<tr>
<th>Cerebral/cardiac involvement</th>
<th>7/2</th>
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<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.1 (7-14.1)</td>
</tr>
<tr>
<td>Platelets (x10⁹/L)</td>
<td>17 (3-70)</td>
</tr>
<tr>
<td>LDH (UI/L)</td>
<td>1255 (411-2316)</td>
</tr>
<tr>
<td>ADAMTS13 activity</td>
<td>&lt; 5% (9/11)</td>
</tr>
<tr>
<td></td>
<td>11 and 23% (2/11)</td>
</tr>
<tr>
<td>Inhibitor or anti-ADAMTS13 Abs</td>
<td>11/11</td>
</tr>
<tr>
<td>ADAMTS13 &gt; 4 rituximab</td>
<td>75% (68-94%) (8)</td>
</tr>
<tr>
<td>Inhibitor/Abs &gt; 4 rituximab</td>
<td>&lt; 50% (3)</td>
</tr>
<tr>
<td>Inhibitor/Abs &gt; 4 rituximab</td>
<td>0/↓ significative</td>
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</tbody>
</table>
Rituximab in acute TTP with suboptimal response

N = 22 patients

Standard treatment initiation

Day 1  Day x  Day x+14  Day 30  Month 3  Month 6  Month 9  Month 12

Day 5 to day x

Rituximab

TPE  R

ADAMTS13 & Abs
Peripheral B cell count

Froissart et al., Crit Care Med 2012
Rituximab in acute TTP with suboptimal response

Rituximab prevents delayed responses to TPE

- Group R+
- Group R-

P=0.03

23%

Mean time to platelet count recovery after the first rituximab infusion: 12±6.7 days

Twice daily TPE
Cyclophosphamide
Splenectomy

Rituximab is not efficient immediately

Froissart et al., Crit Care Med 2012
ADAMTS13 activity and peripheral B cell depletion

- ADAMTS13 activity (%)
- Time following rituximab administration
- Circulating B-lymphocytes (%)
- Anti-ADAMTS13 antibodies (U/ml)

Relapses are prevented during 12 to 18 months

Rituximab does not prevent long term relapses

Froissart et al., Crit Care Med 2012
Rituximab at the acute phase reduces 18-m relapses

Froissart et al., Crit Care Med 2012; Page et al., Blood 2016
Rituximab in association with TPE as a frontline therapy in TTP

A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura

Marie Scully, Vickie McDonald, Jamie Cavenagh, Beverley J. Hunt, Ian Longair, Hannah Cohen, and Samuel J. Machin

1Department of Haematology, University College London Hospital, London, United Kingdom; 2Haemostasis Research Unit, University College London, London, United Kingdom; 3Department of Haematology, St Bartholomew’s and the London Hospital, London, United Kingdom; and 4Department of Haematology, Guys and St Thomas’ National Health Service Foundation Trust, London, United Kingdom

Phase 2 trial – 40 consecutive patients with acquired TTP were included

All patients received rituximab 375 mg/m²/w x4, within 3 days following admission

Rituximab was associated with standard treatment (daily TPE + steroids)

Scully et al., Blood 2011
Rituximab in association with TPE as a frontline therapy in TTP

Platelet count recovered at day-30 in all survivors

Detectable A13 activity in 75% of cases

Undetectable anti-A13 Abs in 75% of cases

Undetectable peripheral B-cells until 6-9 months

Median time to sustained platelet count normalization = 12 d

Scully et al., Blood 2011
Rituximab in association with TPE as a frontline therapy in TTP

Rituximab provides relapse protection for ~ 18 months, but not long term relapses

Should all patients receive rituximab front-line? Risk of overtreatment for a significant nb of patients?

Front-line rituximab is a (very) reasonable indication in the perspective of relapse prevention

Scully et al., Blood 2011
Up to 40% of survivals have a persistent severe (< 10%) ADAMTS13 deficiency after complete remission achievement (particularly < rituximab)

Among them, 38% experience a relapse within a 1-year period

The cumulative incidence of relapse increases with time (*CNR-MAT, in preparation*)

- Therapy-related morbidity/mortality
- Cognitive abnormalities/depression/headache
- Death
- Cost

**Relapse prevention is a major goal**

Howard et al., Transfusion 2006; Ferrari et al., Blood 2007; Sadler, Blood 2008; Viswanathan et al., Br J Haematol 2010; Cataland et al., Am J Hematol 2011; Deford et al., Blood 2013; Saultz et al., Ann Hematol 2015;
Rituximab in relapse prevention

Patients with severe A13 deficiency; otherwise in remission

Rituximab (1-4 infusions)

Severe acquired ADAMTS13 deficiency; TTP otherwise in remission

TTP episode

Day 30  Month 3  Month 6  Month 9  Month 12  Month 18  Month 24

Incidence of relapse?
Response to preemptive rituximab infusions

The median number of TTP episodes before preemptive rituximab administration was 0.57 episode/year (IQR, 0.46-0.7) (≈ 1 relapse/2 y)

After preemptive rituximab administration, the median relapse incidence was not reached [0 episode/year (IQR, 0-0.81)], \( P < .001 \)

Comparison with historical patients w/o rituximab:

<table>
<thead>
<tr>
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<th>R+ group (N = 30)</th>
<th>R- group (N = 18)</th>
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<tbody>
<tr>
<td>Follow-up (months)</td>
<td>36 (24-65)</td>
<td>66 (36-105)</td>
</tr>
<tr>
<td>CI relapses (%)</td>
<td>3 (10)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Relapse incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(relapse/year) (irrespective of f.u. duration)</td>
<td>0 (0-0.81)</td>
<td>0.5 (0.12-0.5)*</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0</td>
<td>2 (11)</td>
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*\( P < .01 \)

Here again, no significant side effects were observed +++
Relapse-free survival

Log-Rank: $P = .049$

Numbers at risk

<table>
<thead>
<tr>
<th>Rituximab</th>
<th>No rituximab</th>
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<tbody>
<tr>
<td>30</td>
<td>18</td>
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<tr>
<td>30</td>
<td>17</td>
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<tr>
<td>24</td>
<td>11</td>
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<td>5</td>
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<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
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</table>
Compounds that require (further) evaluation
Inhibition of Gp1b – vWF: caplacizumab

+ ALX-0681

Inhibitory anti-ADAMTS13 MoAbs

Inhibitor of Gp1b-vWF axis (caplacizumab) is efficient in the treatment and prevention of TTP in a baboon model

Callewaert et al., Blood 2012
Caplacizumab in TTP: the TITAN trial

<table>
<thead>
<tr>
<th>Time to platelet normalisation</th>
<th>Caplacizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median days (95% CI), NO prior PE</td>
<td>3.0 (2.7, 3.9) N = 34</td>
<td>4.9 (3.2, 6.6) N = 35</td>
</tr>
<tr>
<td>Overall hazard rate ratio (95% CI) caplacizumab vs. placebo</td>
<td>2.2 (1.3, 3.8) N = 75</td>
<td></td>
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<tr>
<td>Stratified log-rank test p-value*</td>
<td>0.005</td>
<td></td>
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<table>
<thead>
<tr>
<th>Proportion (number) of subjects (ITT population)</th>
<th>Caplacizumab N = 36</th>
<th>Placebo N = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>81% (29)</td>
<td>46% (18)</td>
</tr>
<tr>
<td>Exacerbation</td>
<td>8% (3)</td>
<td>28% (11)</td>
</tr>
<tr>
<td>Exacerbation and/or relapse up to 1 month follow-up</td>
<td>28% (10)</td>
<td>28% (11)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>2</td>
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Encouraging results ➔ HERCULES trial

Rationale for the use of N-acetylcystein in TTP

The structure, the synthesis and the polymerization process of vWF have homologies with those of mucins

Could the mucolytic properties of NAC be used to limit vWF polymerization and adhesiveness?

Very limited clinical results
Conflicting results were reported as salvage therapy

Li et al., Transfusion 2014
Shortt et al., N Engl J Med 2013
Chapin et al., Br J Haematol 2012

Clinical trials required

Chen et al., J Clin Invest 2011
N-Acetylcysteine is efficient to prevent TTP

The prophylactic administration of NAC in mice KO for A13 prevents TTP

The therapeutic administration of NAC in mice KO for A13 does not reverse TTP features (despite a decrease of HMW vWF)

Tersteeg et al., Blood 2017
The therapeutic administration of NAC in the baboon does not reverse TTP features (despite a decrease of HMW vWF).

NAC cannot dissolve already formed thrombi (accounting for the lack of preclinical efficacy).

Tersteeg et al., Blood 2017
Infusion of recombinant vWF 2000 U/kg

Platelet count after rvWF infusion

Thrombopenia is corrected by rhADAMTS13 administration

Organ damage is corrected by rhADAMTS13 administration

Schiviz et al., Blood 2012 – De Meyer et al., Blood 2012
rADAMTS13 (BAX930) in hereditary TTP

- Phase 1 prospective, open-label, multicenter, dose escalation trial in patients with hereditary TTP

- 15 patients with hTTP were treated with a single injection of rADAMTS13:
  - 5 U/kg (3 patients)
  - 20 U/kg (3 patients)
  - 40 U/kg (9 patients)

  Median age 30 yo (16-41); F/M = 8/7
  12 prophylactic PI; 3 on-demand PI

- rADAMTS13 was well tolerated, no SAE (no anti-A13 related to rADAMTS13)

- ULvWF multimers decreased in the first 24 hours post-dose at the higher doses 20 or 40 U/kg rADAMTS13

  In all groups, changes in vWF multimers were detectable (dose-effect) and accompanied by an increase in the platelet count and a decrease of LDH during the first 96 hours

  These data strongly support the efficacy of rADAMTS13 in hTTP; phase 3 planned

Scully et al., Am Soc Hematol meeting 2016
Plasmocyte-depleting therapies in TTP

Rapid improvement after bortezomib administration

- From 51 consecutive TTP, 5/6 refractory TTP recovered after bortezomib

Deserves further studies
What is the most important to retain?

*Experience-based proof...*
Mrs FO… Da…, 45 yo

Feb, 15th, in the evening: nausea + epigastric pain following a meal of mussels the day before

Feb, 16th: vomiting and hematemesis + jaundice => GP

Feb, 17th in the morning: abdominal ultrasound sonography normal + blood cell count: platelets 6 G/L + Hb 9.6 g/dL

Feb, 17th in the evening: hospitalized in emergency (referred by her GP)

Feb, 18th 4.00 am: schistocytes+++ = treatment by steroids alone for « ITP »

Feb, 18th 8.50 am: sudden death by cardiorespiratory arrest

Diagnosis of TTP made post-mortem
Mrs CA… Ch…, 29 yo

May, 5th: flu-like episode + diarrhea + headache
Consults with her GP
Hb = 6.9 ; platelets = 7 G/L

Hospitalized May, 15th for confusion:
Diagnosis of ITP and treatment with steroids (120 mg Solumedrol x 2/d + IV ig);

Neurologic features persist: referred in the Department of Internal medicine on
May, 19th: diagnosis of TTP;
Treatment with TPE from May, 19th (i.e., with a 2-week delay)

On June, 2\textsuperscript{nd}: sudden death (probable myocardial infarction)
Chronic thrombocytopenia from childhood; no precise etiology, not exhaustively explored. Exsanguinuous-transfusion at day-1 of life for jaundice,

Annual follow-up of platelet count; between 50 and 100 G/L. IVIg + steroids during her 2 pregnancies; thrombocytopenia 5 G/L but otherwise uneventful,

**September, 2014** : increase in serum creatinine level: 112 µmol/l (1.27 mg/dl),

**December, 2014** : consults with a nephrologist (hapto<0.3 g/l ; LDH 400 U/L; proteinuria 0.62 g/d)

**April, 1st, 2015** : renal biopsy: glomerular lesions consistent with a TMA, diagnosis of aHUS retained; eculizumab started…

ADAMTS13 activity <5%; anti-A13 Abs negative, hospitalized on April, 13th 2015 for TPE; immediate response. Probable congenital TTP.
Learning by experience can be painful…

…but it is still more painful not to learn from experience…

To make clinicians aware of TTP diagnosis remains one of the most important issues
Main causes of death in acquired TTP in 2017

We learnt how to manage these patients at the acute phase; and we know how to prevent relapses, but...

- Unrecognized diagnoses
  - Make clinicians more aware of TTP diagnosis
- Fulminant cases dying the first days of management
  - Intensify those patients from diagnosis
Conclusion

Among therapies beyond TPE, rituximab is the one changing the short and long term prognosis of TTP.

The benefit of rituximab relates to the prevention of exacerbations and relapses, and to the shortening in the number of TPE sessions.

Rituximab is not efficient in real time; it does not prevent early deaths.

Intensive regimens including twice-daily TPE may create a « bridge » until rituximab efficacy; in the more desperate cases, consider cyclophosphamide and splenectomy.
Perspectives

An increasing number of promising therapies are now available in the field of TTP (and TMA)

Strategies based on anti-vWF agents and rADAMTS13, in association with anti-B cell agents, should still dramatically improve TTP prognosis by limiting treatment duration, refractoriness and exacerbations

At the acute phase, most deaths occur within 10 days. These patients need to be recognized and their treatment intensified earlier

TTP remains underdiagnosed, with probably a strong impact on survival; to make clinicians aware of TTP diagnosis remains therefore a major goal
The CNR-MAT team