Recent advances in pathogenesis & treatment of aHUS

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Atypical Hemolytic Uremic Syndrome (aHUS)

- Ultra-rare disease: 1-2 cases / million /year
- Affect all ages: 40% older than 18 years old
- Caused by a disregulation of the alternative complement pathway
- MAC = Endothelial damage = Development of TMA
- Clinical suspicion: MHA, Trombocytopenia & organ damage (kidney)
- Clinical diagnosis by exclusion of all other causes of TMA
- Systemic & Severe disease

Early etiological treatment is crucial for aHUS patients
aHUS Pathophysiology
Complement System – Innate Immunity

Activation

Classic/Lectin pathways

Alternative pathway

Opsonization

Inflammation

Lysis

C3b

C3

C3b

C3-convertase (C4b2a)

C3-convertase (C3bBb)

Amplification

MAC (formation)

C5-9 (activation)

Cell Membrane

Terminal pathway


Courtesy Dr Rodríguez de Córdoba
Upon initiation, activation of complement only proceeds if regulation is overcome.

Complement System – Important regulation

Courtesy Dr Rodríguez de Córdoba
aHUS - Pathophysicsiology

A Normal Endothelial Cell


Defenders:

Agressors:
# aHUS – Genetic predisposition

<table>
<thead>
<tr>
<th>Genetic factors</th>
<th>(\text{aHUS})</th>
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<tbody>
<tr>
<td><strong>Genetic factors</strong></td>
<td></td>
</tr>
<tr>
<td>- Mutations</td>
<td>(\text{CFH})</td>
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<tr>
<td></td>
<td>(\text{MCP})</td>
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<tr>
<td></td>
<td>(\text{CFI})</td>
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<tr>
<td></td>
<td>(\text{CFB})</td>
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<td></td>
<td>(\text{C3})</td>
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<tr>
<td></td>
<td>(\text{CFHR1})</td>
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<td></td>
<td>(\text{THBD})</td>
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<tr>
<td>- Polymorphisms</td>
<td>(\text{CFH})</td>
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<tr>
<td></td>
<td>(\text{MCP})</td>
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<tr>
<td></td>
<td>(\text{CFHR1})</td>
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<tr>
<td></td>
<td>(\text{CFHR3})</td>
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<tr>
<td><strong>Autoantibodies</strong></td>
<td>(\text{Factor H})</td>
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</table>

Heterozygous mutations in the C-terminus of factor H are prototypical of aHUS.

Warvicker et al. KI, (1999)
Perez-Caballero et al. AJHG (2001)
Richards et al. AJHG (2001)
Caprioli et al. JASN (2001)
Sanchez-Corral et al. AJHG (2002)
aHUS – Implications of C-terminus CFH mutations

aHUS patients have a specific dysfunction in the protection of cellular surfaces from complement activation.
All aHUS risk factors support defective complement regulation on cell surfaces

Mutations in factor I and MCP, as well as functional characterization of anti factor H antibodies, support defective regulation on self-tissue

Not all aHUS patients have identified genetic mutations

50% of aHUS patients do not have mutations in candidate gene
- Additional risk factors exist

PED_H29; $CFH^{R1210C}$

50% penetrance of aHUS in mutation carriers
- Concurrence of multiple risk factors
New advances – \textit{CFH::CFHR1} hybrid genes

FHL, factor H-like protein; FHR, factor H-related protein
New advances – DGKE-associated aHUS

The lack of discernible complement alterations suggest that DGKE-associated aHUS represents an alternative mechanism leading to TMA that is independent of complement

This has important implications for treatment of early-onset aHUS

27% of pediatric aHUS with onset <1 year

Lemaire M et al. Nat Genet 2013;45:531-6

TMA, thrombotic microangiopathy
Genetic testing always recommended

Allows determination of phenotype–genotype relationships:

- Response to different treatments (supportive care, PE / PI, eculizumab)
- Risk of recurrence after treatment discontinuation
- Risk of recurrence and graft loss after renal transplant:

<table>
<thead>
<tr>
<th>Gen</th>
<th>Risk of death or TCRF in the first episode or one year after</th>
<th>Risk of recurrence</th>
<th>Risk of death or TCRF after 3-5 years</th>
<th>Risk of recurrence after kidney transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>50-70 %</td>
<td>50 %</td>
<td>75 %</td>
<td>75-90 %</td>
</tr>
<tr>
<td>CFI</td>
<td>50 %</td>
<td>10-30 %</td>
<td>50-60 %</td>
<td>45-80 %</td>
</tr>
<tr>
<td>MCP</td>
<td>0-6 %</td>
<td>70-90 %</td>
<td>&lt; 20 %</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>60 %</td>
<td>50 %</td>
<td>75 %</td>
<td>40-70 %</td>
</tr>
<tr>
<td>CFB</td>
<td>50 %</td>
<td>3/3 not with TCRF</td>
<td>75 %</td>
<td>100 %</td>
</tr>
<tr>
<td>THBD</td>
<td>50 %</td>
<td>30 %</td>
<td>54 %a</td>
<td>1 patient</td>
</tr>
<tr>
<td>Anti-FH</td>
<td>30-40 %</td>
<td>40-60 %</td>
<td>35-60 %a</td>
<td>Greater with elevated antibody levels</td>
</tr>
</tbody>
</table>

Rodríguez de Córdoba S et al. Semin Throm Hemost 2014;40:422-30
aHUS: Therapeutic options
Treatment

**Treatment options & Rationale**

**PE / PI**

**PI:** provides normal CFH, CFI, CFB and C3

**PE:**
- Removes mutant CFH, CFI, CFB and C3 (dysfunctional proteins)
- Removes CFH-related protein 1
- Provides functional proteins via fresh-frozen plasma

- Removes antibodies against CFH
- Removes possible *triggers* of endothelial dysfunction and platelet aggregation
- Prevents hypervolaemia
- Prevents hyperproteinaemia

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**Eculizumab**

Classic / lectin pathways

- C3-convertase (C4b2a)

Alternative pathway

- C3-convertase (C3bBb)
- Factor H
- MCP
- Factor I

Terminal pathway

- MAC (formation)
- C5-9 (activation)
- C3b (C3/C5-convertase)

Cell membrane

*aHUS mutations*
Plasmatherapy (PE/PI): Evidences

- Early start of therapy is crucial
- PE is more efficacious than PI in inducing remission and for prevention
- Patients kept in preventive PE / PI (treatment only)
- A rapid decrease in PE / PI increases relapse risk (ESRD)
- Despite PE / PI, organ damage persists in most patients
  - 65% die, need dialysis or present with severe renal damage during the 1st year
- High number of complications associated with the technique
  - Allergies, infections and bleeding

ESRD, end-stage renal disease

Eculizumab clinical development programme

100 patients in total in the prospective clinical trials

Prospective^1^ (26 weeks)
- Study C08-003
  Adult / adolescent (N=20)
- Study C08-002
  Adult / adolescent (N=17)

Prospective (26 weeks)^2^
- Study C10-003
  Paediatrics (N=22)
- Study C10-004
  Adults (N=41)

Retrospective^3^
- Study C09-001
  Patients <18 years (N=19)

Long-term extension studies^4^,^5^
- 86% (32 / 37) of patients continued chronic eculizumab treatment in extension studies

Long-term follow-up study
C11-003^6^: 5 years
March 2012 – December 2017

All aHUS patients

aHUS registry M11-001^7^: treated and not treated
April 2012 – December 2023

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

NEJM: Clinical trials

**C08-003 ‘chronic’**

- Haematological normalisation: 90%
- TMA event-free: 80%
- No new haemodialysis and / or PE / PI: 100%

**C08-002 ‘resistant’**

- Haematological normalisation: 76%
- TMA event-free: 88%
- Reduction in new haemodialysis and / or PE / PI: 100%
  - 4 / 5 patients eliminated haemodialysis

- Long-term improvement in renal function
  - Significant time-dependent mean increase in eGFR
  - Significant improvement in proteinuria

- Earlier tt. was associated with an increased likelihood of improved eGFR

- Similar improved outcomes were observed with or without identified genetic mutations

- Eculizumab was well tolerated

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eGFR, estimated glomerular filtration rate
Early introduction of eculizumab is crucial

Earlier eculizumab was associated with an increased likelihood of improved eGFR to Week 26 (analysis of variation, p=0.03)
Clinical suspicion of aHUS

Paediatric patients
Early administration of eculizumab as the treatment of choice ± support treatment

Adult patients
Early administration of eculizumab (early and intensive PE until start of eculizumab therapy whenever a delay is warranted) ± support treatment

Treatment monitored

- Blood sample taken for later analysis to the start of treatment
- Anti-meningococcus vaccination ± antibiotic prophylaxis

Campistol JM et al. Nefrologia 2013;33:27-45
Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies

Julien Zuber, Fadi Fakhouri, Lubka T. Roumenina, Chantal Loirat and Véronique Frémeaux-Bacchi on behalf of the French Study Group for aHUS/C3G
French Consensus: Treatment recommendations

1st TMA manifestation

- Medical history (malignancies, systemic diseases, pregnancy, medications)
- Physical examination
- Stools: culture, free Shiga toxin or Shiga toxin genes ± LPS serology
- ± ADAMTS13
- HIV serology
- ANA, anti-DNA Ab, APL
- Urinalysis / DAT in children

STEC-HUS

- ADAMTS13 deficiency or
  - Suspected HIV, neoplasia, drug, systemic disease-related HUS

Specific management

1st-line PE therapy

- Plasma resistance after 5 daily PE
- Switch to eculizumab therapy

Unequivocal diagnosis of aHUS and paediatric patients

- 1st-line PE therapy
  - Dependence on PE / PI

Uncertain diagnosis of primary aHUS

- Complement factors (C3, C4, CFH, CFI, CFB)
- MCP expression, anti-CFH Ab

1st-line PE therapy

Zuber J et al. Nat Rev Nephrol 2012;8:643-57
How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uraemic syndrome

Marie Scully\textsuperscript{1} and Tim Goodship\textsuperscript{2}

\textsuperscript{1}Department of Haematology, University College London Hospital, London, and \textsuperscript{2}Department of Renal Medicine, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK
Acute microangiopathic haemolytic anaemia and thrombocytopenia

Acute TMA-TTP, aHUS

Acute renal failure

HUS (or congenital TTP)

ADAMTS13 <10%: exclude congenital TTP

ADAMTS13 ≥10%: ± no evidence of anti-ADAMTS13 IgG antibodies: aHUS after secondary causes excluded

ADAMTS13 <10% + IgG antibodies to ADAMTS13

Immunosuppressive therapy, eg rituximab

ADAMTS13 testing

Samples taken before PE / PI

Plus investigation to exclude secondary cause of TMA

STEC-HUS

TTP

Neurological / cardiological involvement

IgG, immunoglobulin G
Conclusions
Conclusions

- aHUS = disregulation of alternative complement pathway = endothelial damage = TMA

- aHUS is a systemic and severe disease

- If TMA is suspected, we need to make a broad and rapid differential diagnosis

- Eculizumab (monoclonal IgG antibody against C5) in prospective studies involving patients with aHUS effectively interrupted the process of TMA, and was associated in the long term with significant haematological improvements and recovery of renal function
Thank you very much!!
Elevated clinical suspicion of post-transplant TMA
(non-immune haemolytic anaemia + thrombocytopenia + graft dysfunction)

Individualised evaluation of the need for renal biopsy

History of aHUS-caused TCRF
Proable recurrence
(complete differential diagnosis)
Evaluate early use of eculizumab

TMA with no history of aHUS
De novo aHUS
PE + removal of CNI

Secondary TMA
Acute humoral rejection
CMV
BK virus
Aetiological treatment
Evaluate eculizumab in resistant case

CMV, cytomegalovirus;
CNI, calcineurin inhibitor; TCRF, terminal chronic renal failure

Campistol JM et al. Nefrologia 2013;33:27-45
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- Complement factors (C3, C4, CFH, CFI, CFB)
- MCP expression, anti-CFH Ab

1st-line PE therapy

Dependence on PE / PI

Unequivocal diagnosis of aHUS and paediatric patients

1st-line eculizumab therapy

Post-transplantation recurrence of aHUS or the 2nd aHUS relapse involving native kidneys

Zuber J et al. Nat Rev Nephrol 2012;8:643-57