Introduction to pathogenesis and treatment of thrombotic microangiopathies (TMA)

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Evolution of our understanding of the genetic predisposition to aHUS

Perception that aHUS was related to hypocomplementaemia

Realisation of aHUS as a disorder of tissue damage caused by dysregulated complement activation

CFB / I, complement factor B / I; CFHR1, complement factor H-related protein 1; DGKE, diacylglycerol kinase ε; MCP, membrane cofactor protein; RCA, regulator of complement activation; SCR, short consensus repeat

Timeline adapted and updated from Le Quintrec et al 2010

Thrombotic microangiopathy (TMA) is a disorder characterized by an acute syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and variable signs of organ (kidney) injury due to platelet thrombosis in the microcirculation.
Chronic Uncontrolled Complement Activation Leads to Endothelial and End Organ Damage

Clinical Consequences:
- Blood clotting
- Platelet consumption
- Mechanical hemolysis
- Vessel occlusion
- Inflammation
- Ischemia
- Systemic organ complications

Uncontrolled complement activation on cells

Endothelial cells:
- Activation
- Swelling and disruption

Platelets:
- Activation
- Aggregation

Red cells:
- Hemolysis

Leukocytes:
- Activation

Clinical Consequences:

Pathology of Thrombotic Microangiopathy

- Pathological lesion
- Thrombus (clot) formation in microvasculature (small vessels)
- Multiple clots lead to ischemia (deficiency of blood flow to an organ or tissue) and organ dysfunction

- Microangiopathic Hemolysis
  - Presence of shistocytes

Diseases that may have similar clinical presentation to TMA

- Typical haemolytic uraemic syndrome (HUS), also known as Shiga-like toxin-producing Escherichia coli (STEC)-HUS
- aHUS
- Thrombotic thrombocytopenic purpura (TTP)

Zuber J et al. Nat Rev Nephrol 2012;8:643-57;
Causes of systemic TMA

- **aHUS**
  - Genetic defect in complement regulation
  - Chronic, uncontrolled complement activation

- **STEC-HUS**
  - Shiga toxin
    - Direct complement activation
    - Interferes with complement regulation
    - Endothelial damage

- **TTP**
  - Severe deficiency of ADAMTS13 activity
  - Uncleaved long vWF multimeric strings

Systemic TMA:
Multiple thromboses and inflammation throughout the body

Adapted from Zipfel PF et al. Curr Opin Nephrol Hypertens 2010;19:372-8
Diseases that may have similar clinical presentation to TMA

- Typical haemolytic uraemic syndrome (HUS), also known as Shiga-like toxin-producing *Escherichia coli* (STEC) HUS
- aHUS
- Thrombotic thrombocytopenic purpura (TTP)
- Post renal transplant HUS
- Malignancy-related HUS
- Systemic lupus erythematosus (SLE)

HELPP (Haemolysis, Elevated Liver enzymes, Low Platelet count) syndrome (a hypertensive complication of late pregnancy)

Catastrophic antiphospholipid antibody syndrome

Allogeneic stem cell transplantation

Drug-induced nephrotoxicity

Malignant arterial hypertension

Disseminated intravascular coagulation (DIC)

Paroxysmal nocturnal haemoglobinuria (PNH)

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Loss of natural inhibitors leads to chronic uncontrolled complement activation

**Thrombotic microangiopathy: Pathogenesis**

- **COMPLEMENT-MEDIATED TMA**
  - aHUS
  - STEC-HUS

**PREDISPOSING FACTORS**
- Mutations - SNPs
  - (FH, FHRP, FI, C3, MCP)

**PRECIPITATING FACTORS**
- (infections, pregnancy, etc.)
Thrombotic microangiopathy: Pathogenesis

Precipitating factor:
- Infections
- Pregnancy
- Calcineurin inhibitors
- Neuramidase
- Shiga toxin

Predisposing factor:
- CFH/CFHR1
- CFH
- C3
- CFB
- Isolated CFI
- Anti-CFH antibody
- Combined MCP
- Isolated MCP

CFHR, complement factor H-related protein
Etiological classification of thrombotic microangiopathies

Abnormalities of the Complement
- Mutations in CFH, MCP, CFI, THBD, CFB, C3.
- Anti-FH antibodies

TTP (ADAMTS13 activity < 5%)
- Genetic
- Antibodies

Secondary TMA

Pregnancy
- HELLP syndrome
- Postpartum Diseases
- SLE
- Anti-phospholipid syndrome
- Scleroderma
- HIV infection
- Glomerulopathies
- Malignant hypertension
- H1N1 infection (flu A)
- Cancer
- Metabolic diseases

Shiga-like toxin-producing E coli
Strain O157:H7 and other strains, Shigella disenteriae type I, Streptococcus pneumoniae (neuraminidase).

Treatments
- Quinine
- Mitomycin
- Gemcitabine
- Cisplatin
- Ionising radiation
- Interferon
- VEGF and tyrosine kinase
- Ticlopidine and clopidogrel
- Calcineurin inhibitors
- Sirolimus
- Valaciclovir
- Oral contraceptives
- Solid organ and BM TX
The Complement system

Complement has evolved to fight infection, to remove injured self tissue and to amplify/modulate adaptive immunity.

- **Activation**
- **Amplification**
- **Opsonization**
- **Inflammation**
- **Lysis**

**C3**

**C3b**

**C5a**

**C5b**

**C4b**

**C4b2a**

**C3bBb**

**MAC** (formation)

**C5-9**

**C5 (activation)**

**C3/C5-convertase**

**Cell Membrane**

Complement Regulation

Upon initiation, activation of complement only proceeds if regulation is overcome.
Complement and Disease

Defect vs. Excess

Infection
Autoimmunity
Immunecomplexes disease

Chronic
inflammation
Tissue damage

Inherited vs. Non-Inherited

Constitutive dysregulation
(i.e., aHUS, C3G, PNH*)

Complement activation induced by Abs and other causes.
(i.e., MN, IC disease, IgAN, SLE, HA rejection, I/R injury)

* Somatic mutations
## Some disorders associated with complement dysregulation

<table>
<thead>
<tr>
<th>Genetic factors</th>
<th>aHUS</th>
<th>C3 Glomerulopathy</th>
<th>IgAN</th>
<th>SLE</th>
<th>AMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C3GN</td>
<td>DDD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>- Mutations</strong></td>
<td>CFH</td>
<td>CFH</td>
<td>CFH</td>
<td></td>
<td>C2</td>
</tr>
<tr>
<td></td>
<td>MCP</td>
<td>MCP</td>
<td>C3</td>
<td></td>
<td>C4</td>
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<tr>
<td></td>
<td>CFI</td>
<td>CFI</td>
<td>CFHR1</td>
<td></td>
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<tr>
<td></td>
<td>CFB</td>
<td>CFHR1</td>
<td>CFHR2</td>
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<tr>
<td></td>
<td>C3</td>
<td>CFHR3</td>
<td>CFHR3</td>
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<td>CFHR1</td>
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<td>CFHR3</td>
<td>CFHR5</td>
<td>CFHR5</td>
<td>CFHR1</td>
<td>CFHR1</td>
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<tr>
<td><strong>- Polymorphisms</strong></td>
<td>CFH</td>
<td>CFH</td>
<td>CFH</td>
<td>CFHR1</td>
<td>CFHR1</td>
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<tr>
<td></td>
<td>MCP</td>
<td>CFHR1</td>
<td>CFHR1</td>
<td>CFHR3</td>
<td>CFHR3</td>
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<td>CFHR3</td>
<td>CFHR5</td>
<td>CFHR5</td>
<td>CFHR3</td>
<td>CFHR3</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td></td>
<td>Factor H</td>
<td>C3Nef</td>
<td>C3Nef, Factor H</td>
<td></td>
</tr>
<tr>
<td><strong>Environmental factors</strong></td>
<td>Infection</td>
<td>Infection</td>
<td>Infection</td>
<td></td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Immunosupp. drugs</td>
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<tr>
<td></td>
<td>Cancer therapies</td>
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<td></td>
<td>Oral contraceptives</td>
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<td></td>
<td>Pregnancy</td>
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<tr>
<td></td>
<td>Childbirth, etc.</td>
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</tr>
</tbody>
</table>
Both inactivating mutations in genes encoding complement regulators and gain-of-function mutations in genes encoding complement activators have been described.

<table>
<thead>
<tr>
<th>Mutated gene</th>
<th>Protein affected</th>
<th>Consequence</th>
<th>Frequency (%)</th>
<th>Death / ESRD 5–10 years after onset (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>CFH</td>
<td>No binding to epithelium</td>
<td>20–30</td>
<td>70–80</td>
</tr>
<tr>
<td>CFHR1/3</td>
<td>CFHR1, R3</td>
<td>Anti-CFH antibodies</td>
<td>6</td>
<td>30–40</td>
</tr>
<tr>
<td>MCP</td>
<td>MCP (CD46)</td>
<td>No surface expression</td>
<td>10–15</td>
<td>&lt;20</td>
</tr>
<tr>
<td>CFI</td>
<td>CFI</td>
<td>Low level</td>
<td>4–10</td>
<td>60–70</td>
</tr>
<tr>
<td>THBD</td>
<td>THBD</td>
<td>Reduced C3b inactivation</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>CFB</td>
<td>CFB</td>
<td>C3 convertase stabilisation</td>
<td>1–2</td>
<td>70</td>
</tr>
<tr>
<td>C3</td>
<td>C3</td>
<td>Resistance to C3b inactivation</td>
<td>5–10</td>
<td>60</td>
</tr>
<tr>
<td>None identified</td>
<td>?</td>
<td>-</td>
<td>25–30</td>
<td>50(^a,2)</td>
</tr>
</tbody>
</table>

\(^a\)Rate of death or ESRD 3 years after aHUS onset, %

ESRD, end-stage renal disease; THBD, thrombomodulin

aHUS patients have a specific dysfunction in the protection of cellular surfaces from complement activation

FH controls de AP amplification loop and prevents complement activation on host surfaces

**factor H**

- C3b
- RGD
- GAGs
- Hep
- Sialic acid
- GAGs
- Hep
- C3b

**Cofactor activity**

**Decay accelerating activity**

**Ligand and cell surface recognition**

**AP C3-convertase**

**Plasma**

**Cell surface**

**Protection**

**Lysis**
FH is the main regulator of the alternative pathway. It controls complement amplification in plasma and prevents complement activation on host surfaces.
Autoantibodies against CFH are associated with aHUS in a minority of aHUS patients

- Autoantibody (Ab) formation against CFH is found in 7–10% of patients
- These Abs predominately target the C-terminal cell binding recognition domain of CFH and are associated with absence of CFHR1
- The mechanisms leading to CFH-Ab production and disease onset are not completely understood
- Abs against CFI have also been reported
- Recent research has shown that Abs to CD59, CD55, CD46 or CD35 are not associated with aHUS

Diagnosis of aHUS

aHUS is a clinical diagnosis supported by laboratory and exclusion of other TMAs

Thrombotic microangiopathy (TMA) is a disorder characterized by an acute syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and variable signs of organ (kidney) injury due to platelet thrombosis in the microcirculation.
aHUS: systemic, complement-mediated TMA affects multiple vital organs and tissues

Renal
>50% of patients progress to ESRD¹
- Elevated creatinine²
- Proteinuria³
- Oedema,² malignant hypertension⁵
- Decreased eGFR⁶

CNS
≤48% of patients experience neurological symptoms³
- Confusion⁷
- Stroke⁷
- Encephalopathy⁵
- Seizure³

Blood
- Thrombocytopenia¹
- Decreased haptoglobin¹
- Elevated LDH¹
- Decreased haemoglobin¹
- Schistocytes¹

Cardiovascular
≤43% of patients experience cardiovascular symptoms³
- Myocardial infarction⁸
- Hypertension⁹
- Diffuse vasculopathy⁶
- Peripheral gangrene¹⁰

Gastrointestinal
≤30% of patients present with diarrhoea¹¹
- Colitis⁷
- Nausea / vomiting¹²
- Pancreatitis¹²
- Abdominal pain⁷
- Gastroenteritis³
- Liver necrosis³

Pulmonary
- Dyspnoea⁸
- Pulmonary haemorrhage¹³
- Pulmonary oedema⁸

Visual
- Ocular occlusion¹⁴

eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase

TMAs often share similar clinical presentations but differ in the underlying cause

**TTP**
Severe deficiency (≤5%) of ADAMTS13 activity

Severely deficient (≤5%) or no ADAMTS13 activity leaves vWF multimers uncleaved

**aHUS**
Genetic, complement mediated

Genetic defects in activators and / or inhibitors lead to uncontrolled activation of the complement system

**STEC-HUS**
Shiga-toxin induced

Certain bacteria, notably *E. coli*, produce toxins that cause uncontrolled complement activation and direct cell damage

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HUS, haemolytic uraemic syndrome; STEC, Shiga-like toxin-producing *Escherichia coli*; TTP, thrombotic thrombocytopenic purpura; vWF, von Willebrand factor

<table>
<thead>
<tr>
<th>Recommended diagnostic tests (Spanish consensus guidelines) [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEC infection</strong></td>
</tr>
<tr>
<td>Faecal sample (diarrhoea) or rectal swab: STEC cultures (MacConkey for <em>E. coli</em> 0157:H7); PCR for Stx genes 0157:H7 and other serotypes, and other virulent characteristics; ELISA and / or Vero cell tissue culture assay for Stx serum; anti-lipopolysaccharide antibodies for prevalent serotypes</td>
</tr>
<tr>
<td><strong>Pneumococcus infection</strong></td>
</tr>
<tr>
<td>Bacterial culture (generally) of sterile body fluids: direct antiglobulin test (Coombs test), viral test (respiratory), chest X-ray (pleural effusion as a characteristic of most cases), cytochemistry and ligase chain reaction culture in cases secondary to meningitis caused by a pneumococcus</td>
</tr>
<tr>
<td><strong>Altered regulation of the complement system</strong></td>
</tr>
<tr>
<td>C3, C4 (plasma / serum), AH50 CFH, CFI, CFB (plasma / serum) Anti-CFH auto-antibodies Expression of superficial MCP on leucocytes (poly- or mononuclear leucocytes using FACS test) Mutation analysis for CFH, CFI, MCP, C3, CFB ± THBD</td>
</tr>
<tr>
<td><strong>ADAMTS13 deficiency (acquired or hereditary)</strong></td>
</tr>
<tr>
<td>Plasma activity of ADAMTS13 or dose (ELISA) ± inhibitor</td>
</tr>
</tbody>
</table>

AH50, alternative pathway; ELISA, enzyme-linked immunosorbent assay; FACS, fluorescence-activated cell sorting; PCR, polymerase chain reaction; Stx, Shiga toxin
<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommended Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalamine metabolism: methylmalonic aciduria</td>
<td>Amino acid chromatography in plasma / urine samples (hyperhomocysteinaemia, hypomethioninaemia, homocystinuria); organic acid chromatography in urine samples (methylmalonic aciduria); mutation analysis for the gene <em>MMACHC</em></td>
</tr>
<tr>
<td>HIV</td>
<td>Serology, viral load (PCR)</td>
</tr>
<tr>
<td>H1N1 virus</td>
<td>Culture and PCR</td>
</tr>
<tr>
<td>Pregnancy, HELLP syndrome</td>
<td>Pregnancy test, liver enzyme levels (analysis same as lines 3 and 4)</td>
</tr>
<tr>
<td>Other</td>
<td>Anti-nuclear antibodies, lupus anticoagulants and anti-phospholipid antibodies</td>
</tr>
</tbody>
</table>

HELLP, Haemolysis, Elevated Liver enzymes, Low Platelet count; HIV, human immunodeficiency virus
**Differential diagnosis for TMAs: aHUS, TTP and STEC-HUS**

<table>
<thead>
<tr>
<th>Thrombocytopenia(^1-^3)</th>
<th>Microangiopathic haemolysis(^2-^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count &lt;150,000 or &gt;25% decrease from baseline(^1)</td>
<td>Schistocytes(^4-^5) and/or elevated LDH(^4) and/or decreased haptoglobin(^4) and/or decreased haemoglobin(^4)</td>
</tr>
</tbody>
</table>

**AND**

**Plus one or more of the following:**

<table>
<thead>
<tr>
<th>Neurological symptoms(^2-^6-^8)</th>
<th>Renal impairment(^2-^5-^9)</th>
<th>GI symptoms(^5-^7-^13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion(^2-^6) and/or seizures(^2-^6) and/or other cerebral abnormalities(^2-^9)</td>
<td>Elevated creatinine(^2-^10) and/or decreased eGFR(^2-^10) and/or elevated blood pressure(^1) and/or abnormal urinalysis(^1)</td>
<td>Diarrhoea +/- blood(^1) and/or nausea / vomiting(^1) and/or abdominal pain(^1) and/or gastroenteritis(^4)</td>
</tr>
</tbody>
</table>

Evaluate ADAMTS13 activity and Shiga-toxin / EHEC* test\(^3\-^15\-^16\)

*Shiga-toxin / EHEC test is warranted with history / presence of GI symptoms

**EHEC, enterohaemorrhagic *Escherichia coli*; GI, gastrointestinal**

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1. Alexion Pharmaceuticals, Inc. Data on file;
2. Loirat C, Frémeaux-Bacchi V. Orphanet J Rare Dis 2011:6:60;
Differential diagnosis for TMAs: aHUS, TTP and STEC-HUS

Thrombocytopenia\(^1\)\(^-\)\(^3\)
Platelet count <150,000 or
>25% decrease from baseline\(^1\)

Microangiopathic haemolysis\(^2\)\(^-\)\(^4\)
Schistocytes\(^4\)\(^,\)\(^5\) and / or
elevated LDH\(^4\) and / or
decreased haptoglobin\(^4\) and / or
decreased haemoglobin\(^4\)

AND

Plus one or more of the following:

Renal impairment\(^2\)\(^,\)\(^5\)\(^,\)\(^9\)
Elevated creatinine\(^2\)\(^,\)\(^10\) and / or
decreased eGFR\(^2\)\(^,\)\(^10\) and / or
elevated blood pressure\(^11\) and / or
abnormal urinalysis\(^12\)

Gastrointestinal symptoms\(^5\)\(^,\)\(^7\)\(^,\)\(^13\)
Diarrhoea +/- blood\(^14\) and / or
nausea / vomiting\(^13\) and / or
abdominal pain\(^13\) and / or
gastroenteritis\(^4\)\(^,\)\(^14\)

Neurological symptoms\(^2\)\(^,\)\(^6\)\(^-\)\(^8\)
Confusion\(^2\)\(^,\)\(^6\) and / or
seizures\(^2\)\(^,\)\(^6\) and / or
other cerebral abnormalities\(^2\)\(^,\)\(^9\)

Evaluate ADAMTS13 activity and Shiga-toxin / EHEC* test\(^3\)\(^,\)\(^15\)\(^,\)\(^16\)

While waiting for ADAMTS13 results, a platelet count >30,000 mm\(^3\) or SCr >150–200 µmol/L
(>1.7–2.3 mg/dL) almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)\(^17\)

<5% ADAMTS13 activity\(^15\)\(^,\)\(^16\)

≤5% ADAMTS13 activity\(^15\)\(^,\)\(^16\)

>5% ADAMTS13 activity\(^14\)

Shiga-toxin / EHEC positive\(^18\)

TTP

aHUS

STEC-HUS

*Shiga-toxin / EHEC test is warranted with history / presence of GI symptoms

This pathway is intended as educational information for healthcare providers. It does not replace a healthcare professional’s judgement or clinical diagnosis

Plasma therapy, a common treatment option for TMA, does not address the underlying cause of aHUS.

<table>
<thead>
<tr>
<th>Affected protein</th>
<th>Short-term outcome of PE / PI*</th>
<th>Long-term outcome of PE / PI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>60%</td>
<td>Death or ESRD: 70–80%</td>
</tr>
<tr>
<td>CFHR1, R3</td>
<td>70–80%</td>
<td>ESRD: 30–40%</td>
</tr>
<tr>
<td>MCP</td>
<td>No definitive indication for therapy</td>
<td>Death or ESRD: &lt;20%</td>
</tr>
<tr>
<td>CFI</td>
<td>30–40%</td>
<td>Death or ESRD: 60–70%</td>
</tr>
<tr>
<td>CFB</td>
<td>30%</td>
<td>Death or ESRD: 70%</td>
</tr>
<tr>
<td>C3</td>
<td>40–50%</td>
<td>Death or ESRD: 60%</td>
</tr>
<tr>
<td>THBD</td>
<td>60%</td>
<td>Death or ESRD: 60%</td>
</tr>
</tbody>
</table>

*Short-term outcome was defined as the rate response to short-term plasma therapy; long-term outcome was defined as the outcome 5–10 years after onset.

Eculizumab blocks terminal complement

Complement cascade

- Monoclonal antibody binds with high affinity to C5
- Terminal complement activity is blocked
- Proximal functions of complement remain intact
  - Weak anaphylatoxin
  - Immune complex clearance
  - Microbial opsonisation

2. Alexion Europe SAS. Eculizumab Summary of Product Characteristics, 03/2014
Eculizumab clinical development programme (2009 onwards)

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

# Overview of findings in the pivotal eculizumab trials

**C08-003 ‘long duration of aHUS and CKD’**

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

**C08-002 ‘progressing TMA’**

- 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 treatment was associated with an increased likelihood of improved eGFR
- Similar improved outcomes were observed in patients with or without identified genetic mutations
- Eculizumab was well tolerated

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Earlier treatment with eculizumab leads to greater improvement in renal function

Earlier intervention with eculizumab was associated with greater improvement in eGFR through week 52 (ANOVA with clinical disease manifestation as covariate, p=0.03)

Median duration of aHUS current clinical manifestation to study was 0.75 months (range, 0.2–4.0)

C10-004 (adult patients): primary and secondary end points met by most patients

<table>
<thead>
<tr>
<th>Metric</th>
<th>Percentage</th>
<th>Median days to end point (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response (primary)</td>
<td>73%</td>
<td>56 (2–147)</td>
</tr>
<tr>
<td>Haematological remission</td>
<td>88%</td>
<td>55 (2–146)</td>
</tr>
<tr>
<td>Platelet count normalisation</td>
<td>96%</td>
<td>8 (0–84)</td>
</tr>
<tr>
<td>Modified TMA response</td>
<td>56%</td>
<td>57 (2–147)</td>
</tr>
</tbody>
</table>

a Defined as platelet count and LDH normalisation (>150 × 10^9/L and < ULN, respectively) together with maintenance of renal function (<25% increase from baseline in SCr);
b Defined as platelet count and LDH normalisation ULN, upper limit of normal

Fakhouri F et al. American Society of Nephrology Kidney Week 2013, abstract 5593
C10-004: significant and continued improvement in eGFR with ongoing eculizumab treatment

Mean change from baseline in eGFR at Week 26: **29.3 mL/min/1.73 m²**

- **Dialysis could be discontinued**
  - 20 / 24 (83%) of patients on dialysis at baseline could discontinue dialysis
  - 15 / 17 (88%) patients not on dialysis at baseline, remained dialysis free through the study evaluation period

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f**Mean change from baseline in eGFR at Week 26**

<table>
<thead>
<tr>
<th>Study week</th>
<th>Mean change from baseline (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
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- †p<0.05
- #p<0.001
- *p<0.0001

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*Mean (SD) eGFR at baseline: 17.3 (12.05); mean (SD) eGFR at Week 25: 47.0 (24.35)
Before eculizumab, 100% of patients had eGFR <60 mL/min/1.73 m²
SD, standard deviation

Fakhouri F et al. American Society of Nephrology
Kidney Week 2013, abstract 5593
C10-003 (paediatric patients): primary and secondary end points were met by most patients

- No new safety concerns were reported; similar AE profile as in adults

Median days to
end point (range)
- Platelet count normalisation: 7.0 (1.0–80.0)
- Haematological remission: 55.0 (1.0–153.0)
- Complete TMA response (primary): 60.0 (7.0–153.0)

*TMA response defined as haematological remission and ≥25% improvement in eGFR

Greenbaum LA et al. Poster 2191 presented at American Society of Haematology 2013
C10-003 (paediatric patients): positive renal outcomes at 26 weeks

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
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<tbody>
<tr>
<td>eGFR increase from baseline, (mL/min/1.73 m²), LS mean (95% CI)</td>
<td>64 (50; 79), p&lt;0.0001 (Week 25)</td>
</tr>
<tr>
<td>eGFR improvement from baseline, (≥15 mL/min/1.73 m²), n / N (%)</td>
<td>19 / 22 (86)</td>
</tr>
<tr>
<td>SCr ≥25% decrease from baseline, n / N (%)</td>
<td>16 / 22 (73)</td>
</tr>
<tr>
<td>Patients on dialysis at baseline who discontinued dialysis, a n / N (%)</td>
<td>9 / 11 (82)</td>
</tr>
</tbody>
</table>

a1 of 11 patients on dialysis at baseline discontinued prior to the 1st dose; bLast available data point from Day 154 or 175

Greenbaum LA et al. Poster 2191 presented at American Society of Haematology 2013
C10-004: AE findings were consistent with other eculizumab studies

<table>
<thead>
<tr>
<th>AEs occurring in ≥15%</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>C10-004 [n=41]</td>
<td></td>
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<tr>
<td>Headache</td>
<td>15 (37)</td>
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<tr>
<td>Diarrhoea</td>
<td>13 (32)</td>
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<tr>
<td>Oedema (peripheral)</td>
<td>9 (22)</td>
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<tr>
<td>Cough</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (17)</td>
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<tr>
<td>Nasopharyngitis</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>7 (17)</td>
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</tbody>
</table>

- Most AEs were mild or moderate
- 2 patients had meningococcal infection
  - 1 patient recovered and discontinued from the study due to meningococcal infection
  - The 2nd patient recovered and remained on eculizumab treatment
- No new safety concerns
- No deaths

AE, adverse event

1. Fakhouri F et al. American Society of Nephrology Kidney Week 2013, abstract 5593
Revisión

Actualización en síndrome hemolítico urémico atípico: diagnóstico y tratamiento. Documento de consenso

Josep M. Campistol a,*, Manuel Arias b, Gema Ariceta c, Miguel Blasco a, Laura Espinosa d, Mario Espinosa e, Josep M. Grinyó f, Manuel Macía g, Santiago Mendizábal h, Manuel Praga i, Elena Román h, Roser Torra j, Francisco Valdés k, Ramón Vilalta c y Santiago Rodríguez de Córdoba l

Document approved by:

- Spanish Society of Nephrology (SEN)
- Spanish Transplant Society (SET)
- Spanish Association of Paediatric Nephrology (AENP)
Treatment for aHUS: Spanish consensus recommendations

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 whenever a delay in treatment is warranted) ± support treatment

Treatment monitored

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

Campistol JM et al. Nefrologia 2013;33:27-45
aHUS: what we know today

- aHUS is a genetic, life-threatening, catastrophic disease of chronic progressive TMA that affects both adults and children.
- Chronic, uncontrolled complement activation underlies the pathology of aHUS, with disease development requiring the presence of a combination of an endothelial insult and genetic factors.
- aHUS has a systemic impact and affects multiple organ systems – urgent treatment is crucial.
- Eculizumab inhibits complement-mediated TMA and benefits are maintained with long-term therapy.
- Recent prospective results from C10-003 and C10-004 confirm the findings of the 2 pivotal trials of eculizumab, and support the recent recommendations of eculizumab as 1st-line treatment in adults once an unequivocal diagnosis is made and in children.
Thank you !!!!