Eculizumab in aHUS: where do we stand in 2016

Prof. Fadi Fakhouri
Dept. of nephrology and immunology, CHU de Nantes.
INSERM UMR S-1064
Thrombotic microangiopathy: evolving concepts

- Complement dysregulation-associated TMA
  - aHUS

- ADAMTS13 deficiency-associated TMA
  - TTP

- Post infection TMA
  - Pneumococcal
  - HIV

- Drug-mediated TMA
  - CNI, anti VEGF

- TMA of unknown mechanism

- Coagulation mediated-TMA
  - DGKe

- VitB12 metabolism mediated TMA

Adapted from Fakhouri, Nature Rev Nephrology, 2009
Complement system

C3 convertase → C3 → C3b → C5 convertase → C5 → C6,7,8,9 → C5b → iC3b → sMAC
Thrombotic microangiopathy

CAP dysregulation in aHUS

Noris M, NEJM 2009
65% of patients were treated with plasma exchange / plasma infusion
Eculizumab: humanised 1st-in-class anti-C5 antibody

Human framework regions
- No mutations
- Germline

Complementarity determining regions (murine origin)

Human IgG₂ heavy chain constant region 1 and hinge (eliminates Fc receptor binding)

Human IgG₄ heavy chain constant regions 2 and 3 (eliminates complement activation)
Eculizumab dosing regimen

Adults and children ≥40 kg: Induction: 900 mg weekly for 4 doses; Maintenance: 1200 mg at week 5, then 1200 mg every 2 weeks.
Children < 40 Kg: Dose adjusted to weight.

Monitoring of complement blockade

CH50 <10% (or AP50 < 10%)
Eculizumab trough level >100 mg/ml

Meningococcal vaccination

Mandatory before eculizumab initiation.

Antibioprophylaxis

Methylpenicillin (in case of allergy to penicillin, macrolides).
Mandatory during the first 2 weeks after vaccination.
Maintained throughout eculizumab treatment (and up to 2 months after discontinuation) in some countries.

Patients’ education and information card.
The largest prospective study with eculizumab in aHUS (adults)

n= 41
≥18 years

Inclusion criteria

Plts <150 × 10^9/L
Hb ≤ LLN
LDH ≥1.5 × ULN
SCr ≥ ULN

No specification for PE / PI prior to enrolment

ADAMTS13 activity > 5%

No evidence of STEC-HUS

Identification of C genes mutations / polymorphisms or autoAbs, not required.
Primary outcome:
- Platelet $\geq 150 \times 10^9/L$
- LDH $\leq$ ULN
- $<25\%$ increase in SCr from baseline

Secondary outcomes included:
- Modified complete TMA response
  - Plts + LDH normalisation
  - $\geq 25\%$ decrease in SCr from baseline
- Haematological normalisation (Plts and LDH normalisation)
- Change from baseline in eGFR

n=41

Identified complement genes mutation or autoantibody, n (%) 20 (49)
Median duration of current clinical manifestation, months (range) 0.5 (0.0–19.2)
Mean SCr, $\mu$mol/L (SD) 411.0 (264.6)
Mean eGFR, mL/min/1.73 m² (SD) 17.3 (12.1)
Dialysis at baseline, n (%) 24 (59)
Prior renal transplant, n (%) 9 (22)
Terminal Complement Inhibitor Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial

Fadi Fakhouri, MD, PhD,1 Maryvonne Hourmant, MD, PhD,1 Josep M. Campistol, MD,2 Spero R. Cataland, MD,3 Mario Espinosa, MD,4 A. Osama Gaber, MD,5 Jan Menne, MD,6 Enrico E. Minetti, MD,7 François Provôt, MD,8 Eric Rondeau, MD, PhD,9 Piero Ruggenenti, MD,10 Laurent E. Weekers, MD,11 Masayo Ogawa, MD,12 Camille L. Bedrosian, MD,12 and Christophe M. Legendre, MD13

20 / 24 (83%) of patients on dialysis at baseline could discontinue dialysis

Study week

F. Fakhouri, ASN  2013

AJKD 2016
Terminal Complement Inhibitor Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial

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24 patients on dialysis at screening

- 5 discontinue dialysis prior to first dose
- 19 remain on dialysis

17 patients not on dialysis at screening

- 17/23 (74%)

First dose

- 15 discontinue dialysis before week 26
- 4 remain on dialysis at week 26

- 4 initiate new dialysis
  - 2 discontinue dialysis before week 26
  - 2 remain on dialysis at week 26

Figure 4. Dialysis use at baseline and during the study.
<table>
<thead>
<tr>
<th></th>
<th>Eculizumab-treated aHUS cases (n=18)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>13 (72%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>27 (19-53)</td>
<td>0.4</td>
</tr>
<tr>
<td>Complement genes mutations</td>
<td>13 (72%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>12 (63%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Platelet count &gt; 150 G/L</td>
<td>4 (21%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Plasma exchanges</td>
<td>15 (83%)</td>
<td>0.1</td>
</tr>
<tr>
<td>End-stage renal disease within</td>
<td>3 (17%)</td>
<td>0.02</td>
</tr>
<tr>
<td>3m of aHUS flare</td>
<td>2/8 (25%)</td>
<td>0.04</td>
</tr>
<tr>
<td>End-stage renal disease at 1 year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Insights from use in clinical practice of eculizumab in adult patients with aHUS affecting the native kidneys: an analysis of 19 cases

(2004-2008)

<table>
<thead>
<tr>
<th></th>
<th>Historical controls (n=41)</th>
<th>Eculizumab-treated aHUS cases (n=18)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>28 (68%)</td>
<td>13 (72%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>34 (18-85)</td>
<td>27 (19-53)</td>
<td>0.4</td>
</tr>
<tr>
<td>Complement genes mutations</td>
<td>28 (68%)**</td>
<td>13 (72%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>29 (71%)</td>
<td>12 (63%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Platelet count &gt; 150 G/L</td>
<td>6/36 (17%)</td>
<td>4 (21%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Plasma exchanges</td>
<td>24/38 (63%)**</td>
<td>15 (83%)</td>
<td>0.1</td>
</tr>
<tr>
<td>End-stage renal disease within 3m of aHUS flare</td>
<td>20 (46%)</td>
<td>3 (17%)</td>
<td>0.02</td>
</tr>
<tr>
<td>End-stage renal disease at 1 year</td>
<td>23/36 (63%)</td>
<td>2/8 (25%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Insights from use in clinical practice of eculizumab in adult patients with aHUS affecting the native kidneys: an analysis of 19 cases

Early Ecu intiation = Better renal outcome

### Percentage of patients on chronic dialysis in the 4 trials of eculizumab, compared to the French cohort (pre-eculizumab)

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>French cohort (N=125)</th>
<th>Trial 1 (N=17)</th>
<th>Trial 2 (N=20)</th>
<th>Trial 4 (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode</td>
<td>46%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td>6%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>1 year</td>
<td>56%</td>
<td>6%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>2 years</td>
<td></td>
<td>12%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>64%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

French cohort: Fremeaux-Bacchi *et al*, CJASN 2013
Insights from the use in clinical practice of eculizumab in adult patients with aHUS affecting the native kidneys: an analysis of 19 cases.
Defining a new clinical picture of aHUS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children</th>
<th>Adults</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>89</td>
<td>125</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female/male (n/n)</td>
<td>42/47</td>
<td>93/32</td>
<td></td>
</tr>
<tr>
<td>Mean age at onset (yr)</td>
<td>1.5 (0 to &lt;15)</td>
<td>31 (15-85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Familial HUS history, n (%)</td>
<td>24 (26.9)</td>
<td>18 (14.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Triggering events, n (%)</td>
<td>42 (47)</td>
<td>41 (33)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35 (39)</td>
<td>19 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>7 (8)</td>
<td>1 (1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>18/93 females (19.3)</td>
<td>10 (8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Neurologic involvement, n (%)</td>
<td>14 (16)*</td>
<td>10 (8)</td>
<td></td>
</tr>
<tr>
<td>Mean serum creatinine (μmol/L)</td>
<td>257 (28-990) (n=82)</td>
<td>640 (111-2408) (n=113)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis required, n (%)</td>
<td>48/81 (59)</td>
<td>93/115 (81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets count, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 × 10^3/L</td>
<td>12/81 (15)</td>
<td>15/93 (16)</td>
<td>0.78</td>
</tr>
<tr>
<td>100-150 × 10^3/L</td>
<td>9/81 (11)</td>
<td>22/93 (24)</td>
<td>0.02</td>
</tr>
<tr>
<td>50-99 × 10^3/L</td>
<td>26/81 (32)</td>
<td>31/93 (33)</td>
<td>0.04</td>
</tr>
<tr>
<td>&lt; 50 × 10^3/L</td>
<td>34/81 (42)</td>
<td>25/93 (27)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean hemoglobin (g/dl)</td>
<td>6.3 (3–12) (n=84)</td>
<td>7.2 (5–11.8) (n=93)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hemoglobin &gt; 10 g/dl, n (%)</td>
<td>5/84 (6)</td>
<td>10/93 (11)</td>
<td>0.16</td>
</tr>
<tr>
<td>Complete triad, n (%)</td>
<td>60/81 (74)</td>
<td>77/93 (83)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Values are given as means with ranges in parentheses or as percentages. HUS, hemolytic uremic syndrome.

*In children, extrarenal manifestations also included pancreatitis (increase of pancreatic enzymes with or without clinical/radiologic signs) in six cases (7%), hepatitis (increase in hepatic enzymes) in five cases (6%), multiorgan failure in three cases (3%), intra-alveolar hemorrhage in two cases (2%), and pericarditis in one case (1%). Extrarenal manifestations other than neurologic are not documented in adults.

*Complete triad: hemoglobin < 10 g/dl plus platelet count < 150 G/L plus serum creatinine above the upper limit of normal.
Recommendations for managing adult patients with aHUS

Who should be treated with eculizumab?
Any patient with a clinical presentation of aHUS should be considered as a candidate
The spectrum of indications encompasses aHUS involving either native or transplanted kidneys as well as aHUS with incomplete clinical presentation

- ADAMTS13 deficiency
- Suspected HIV
- Neoplasia, Drugs
- Systemic disease-related HUS

First-line PE therapy

- Uncertain diagnosis of primary aHUS
- Complement factors (C3, C4, CFH, CFI, CFB)
- MCP expression, anti-CFH Ab

First-line PE therapy

- Plasma resistance after 5 PE
- Dependence on plasma
- No constant upward trend of Plts (particularly if Plts < 150 G/l)
or no constant downward trend of LDH (particularly if LDH > ULN)or absence of decrease Scr > 25%

Switch to eculizumab therapy

Unequivocal diagnosis of aHUS

First-line eculizumab
Absence of complement genes mutations does not exclude aHUS

<table>
<thead>
<tr>
<th>aHUS Phase</th>
<th>Overall</th>
<th>Mutations</th>
<th>No mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced serum C3</td>
<td>Acute 10/18 5/9</td>
<td>5/9</td>
<td></td>
</tr>
<tr>
<td>Increased serum C5α</td>
<td>Acute 9/19 3/10</td>
<td>6/9</td>
<td></td>
</tr>
<tr>
<td>Increased sC5b-9</td>
<td>Acute 10/19 4/10</td>
<td>6/9</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Noris et al., *Blood*, 2014
Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS

Roxanne Cofield, Anjli Kukreja, Krystin Bedard, Yan Yan, Angela P. Mickle, Masayo Ogawa, Camille L. Bedrosian and Susan J. Faas

Blood, 2015
Normal complement levels do not exclude aHUS diagnosis
Complement activation and aHUS

A hypothesis...

Threshold for aHUS onset

Individual variability

Precipitating factors

Complement induced endothelial damage

C genes mut +at-risk C genes polymorphisms

at-risk C genes polymorphisms

no mut no polymorphisms

Pregnancy

Infection
Eculizumab rescues distal ischaemic manifestations of aHUS

Ariceta et al. AJKD 2012
28-day-old child, 3.6 kg
- No mutation
- Leg skin necrosis, intestinal perforation
- **Eculizumab → remission within 3 days**
- Recovery of skin lesions and renal function
- **Follow-up 18 months, Sceatinine 23 μmol/L, remission**

Malina et al. Pediatrics 2013
2-month-old child
- ESRD, multiple relapses despite plasma infusions
- C3 gain of function mutation
- At 9 months, acute ischaemia of feet and hands, resistant to PE
- **Eculizumab → immediate reversal of distal ischaemia**
- **Follow-up 22 months, remission**

Eculizumab
Day 21, then every 3 weeks
Ulcerative-necrotic skin lesions in aHUS
Recovery under eculizumab

Before eculizumab

19-year-old man (no mutation)
• On dialysis
• **Skin lesions for 10 months** + thrombocytopenia
• Skin biopsy: TMA lesions
• **Recovery after one dose of eculizumab**

After eculizumab

19-year-old man (factor H mutation)
• Functioning kidney graft under PE/PI
• **Skin lesions for several months**
• Switch from PE to eculizumab
• **Improvement of skin lesions after first dose with further complete reversal**
Eculizumab appears efficient to rescue CNS involvement in aHUS
10 case reports (PE resistant:8; 1st line eculizumab:2)

<table>
<thead>
<tr>
<th>Author</th>
<th>Age, yrs (Mutation/Anti-FH)</th>
<th>Neurological manifestations</th>
<th>MRI</th>
<th>Time to eculizumab initiation (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pu 2013</td>
<td>85 (None)</td>
<td>Seizures, mental disturbances</td>
<td>ND</td>
<td>18</td>
<td>Improvement over 2 weeks</td>
</tr>
<tr>
<td>Salem 2012</td>
<td>66 (C3)</td>
<td>Seizures, mental disturbances, coma</td>
<td>Focal lesions</td>
<td>3</td>
<td>Awoke and verbal after 8 weeks Nearly complete recovery</td>
</tr>
<tr>
<td>Beye 2013</td>
<td>64 (None)</td>
<td>Status epilepticus, focal defects, nystagmus, confusion</td>
<td>Normal CTS</td>
<td>9</td>
<td>Improvement within 24 hours Full recovery</td>
</tr>
<tr>
<td>Ohanian 2011</td>
<td>50 (None)</td>
<td>Seizures, unresponsiveness</td>
<td>Right parietal infarction</td>
<td>3</td>
<td>Improvement after 1 week Full recovery</td>
</tr>
<tr>
<td>Avila 2015</td>
<td>27 (None)</td>
<td>Decreased intellectual performance, self-limited episode of loss of consciousness</td>
<td>Several high-intensity subcortical white matter lesions in frontal lobes</td>
<td>7</td>
<td>Full recovery within a few days</td>
</tr>
<tr>
<td>Chaudhary 2014</td>
<td>20 (None)</td>
<td>Seizures, lethargy</td>
<td>ND</td>
<td>42</td>
<td>Slow initial improvement (subtherapeutic doses) Full recovery after dose increase</td>
</tr>
<tr>
<td>Gulleroglu 2013</td>
<td>11 (None)</td>
<td>Seizures, visual loss, confusion</td>
<td>Bilateral occipital and posterior parietal hyperdensities/oedema</td>
<td>2</td>
<td>Improvement after 4 days Full recovery after 1 month</td>
</tr>
<tr>
<td>Gulleroglu 2013</td>
<td>6 (MCP)</td>
<td>Seizures, visual loss</td>
<td>Bilateral occipital and posterior parietal hyperdensities</td>
<td>&lt;1</td>
<td>Normal vision within 24 hours Full recovery after 5 weeks</td>
</tr>
<tr>
<td>Diamante Chiodini 2014</td>
<td>8 (Anti-FH)</td>
<td>Confusion, delirium Persistant psychocognitive impairment under PE/PI</td>
<td>Multifocal hypersignals</td>
<td>20</td>
<td>Full recovery within 2 weeks</td>
</tr>
<tr>
<td>Hu 2013</td>
<td>1.7 (None)</td>
<td>Seizures, hemiparesis, lethargy, unresponsiveness</td>
<td>Subtle bilateral anomalies</td>
<td>&lt;1</td>
<td>Improvement over 3 weeks Full recovery with residual weakness of right thumb/index</td>
</tr>
</tbody>
</table>
Eculizumab appears efficient to rescue ischemic cardiomyopathy in aHUS
4 case reports in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Age, yrs (mutation/anti-FH)</th>
<th>Cardiac manifestations</th>
<th>Response to PE</th>
<th>Time to eculizumab initiation (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vilalta 2012</td>
<td>1.5 (CFH)</td>
<td>Day 60 under PE: Dilated cardiomyopathy Cardiorespiratory arrest</td>
<td>Resistance to PE</td>
<td>80</td>
<td>Improvement of cardiac function over 6 days. Subsequent full recovery.</td>
</tr>
<tr>
<td>Hu 2013</td>
<td>1.6 (None)</td>
<td>Day 0: Dilated cardiomyopathy EF 30% Cardiovascular instability, hypotension</td>
<td>First line eculizumab</td>
<td>&lt; 12 hours</td>
<td>Recovery over 9 days</td>
</tr>
<tr>
<td>Diamante Chiodini 2014</td>
<td>8 (Anti-FH)</td>
<td>Day 20 under PE: Dilated cardiomyopathy EF 37% Repolarization anomalies High troponine level</td>
<td>Resistance to daily PE + plasma intolerance</td>
<td>37</td>
<td>Normalization of LV volume and function over 2 weeks</td>
</tr>
<tr>
<td>Michaux 2014</td>
<td>11 days (Homozygous CFH)</td>
<td>Day 11: Myocardial incompetence Increased troponin Hemodynamic instability Respiratory failure</td>
<td>PE not tolerated</td>
<td>2</td>
<td>Recovery within a few days</td>
</tr>
</tbody>
</table>
aHUS: a chronic disease

Relapse pattern in adult aHUS patients

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>CFH</th>
<th>CFI</th>
<th>MCP</th>
<th>C3</th>
<th>No Mut</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=66)</td>
<td>(n=20)</td>
<td>(n=8)</td>
<td>(n=6)</td>
<td>(n=7)</td>
<td>(n=21)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F-up (M)</th>
<th>52</th>
<th>55</th>
<th>58</th>
<th>11</th>
<th>50</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1R</td>
<td>35%</td>
<td>30%</td>
<td>38%</td>
<td>33%</td>
<td>71%</td>
<td>33%</td>
</tr>
<tr>
<td>1st R &lt; 1y</td>
<td>29%</td>
<td>30%</td>
<td>38%</td>
<td>33%</td>
<td>43%</td>
<td>25%</td>
</tr>
<tr>
<td>1st R &gt; 1y</td>
<td>6%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>28%</td>
<td>5%</td>
</tr>
<tr>
<td>R &gt; 1y</td>
<td>20%</td>
<td>19%</td>
<td>25%</td>
<td>33%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
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Fremeaux-Bacchi et al, CJASN 2013
Thrombotic microangiopathy: evolving concepts

- Complement dysregulation-associated TMA
- aHUS
- Post infection TMA
  - Pneumococcal
  - HIV
- Drug-mediated TMA
  - CNI, anti VEGF
- ADAMTS13 deficiency-associated TMA
- TTP
- Coagulation mediated-TMA
  - DGKε
- BMT-TMA
- VitB12 metabolism mediated TMA
- TMA of unknown mechanism

Adapted from Fakhouri, Nature Rev Nephrology, 2009
TMA in pregnancy

F, 34 y
2nd uneventful pregnancy
3 weeks PP
SCr 650 mmol/l
Plts 110 G/L
LDH 2.5 ULN
Hb 10 g/dl
Haptoglobin undetectable
Schizocytes neg
Puria 2 g/l

1 woman/5 had aHUS during pregnancy
79% of cases occurred during the post partum

Fakhouri F, JASN, 2010
## Complement dysregulation-related TMA in pregnancy

**Fakhouri F, JASN, 2010**

<table>
<thead>
<tr>
<th></th>
<th>Patients with P-associated aHUS (n=21)</th>
<th>Patients with aHUS non related to pregnancy (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at aHUS onset (years)</td>
<td>26 ± 5</td>
<td>33 ± 12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nb of pregnancies</td>
<td>2 ± 0.8</td>
<td>2.3 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Nb of patients reaching ESRD &lt; 6 months after aHUS</td>
<td>11 (52%)</td>
<td>20 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of patients reaching ESRD at last follow-up</td>
<td>16 (76%)</td>
<td>26 (74%)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of patients with complement abnormality</td>
<td>18 (86%)</td>
<td>26 (74%)</td>
<td>NS</td>
</tr>
<tr>
<td>CFH</td>
<td>10 (48%)</td>
<td>14 (40%)</td>
<td>NS</td>
</tr>
<tr>
<td>CFI</td>
<td>3 (14%)</td>
<td>6 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>MCP</td>
<td>1 (5%)</td>
<td>3 (8.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>C3</td>
<td>2 (9.5%)</td>
<td>1 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>FB</td>
<td>0 (0%)</td>
<td>2 (5.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>More than one mutation</td>
<td>2 (9.5%)</td>
<td>1 (3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
TMA in pregnancy

F, 34 y
2nd uneventful pregnancy
3 weeks PP
SCr 650 mmol/l
Plts 110 G/L
LDH 2.5 ULN
Hb 10 g/dl
Haptoglobin undetectable
Schizocytes neg
Puria 2 g/l

P-aHUS = an aHUS precipitated by pregnancy.

Fakhouri F, JASN, 2010
Thrombotic microangiopathy: evolving concepts

Secondary TMA / TMA-like disorders

Kidney-transplantation related TMA

« CFH or CFI gene mutations found in 7/24 patients (29%) »
Le Quintrec M, AJT 2008
Complement as an amplifying process in secondary HUS.

**Mitomycin C**  
Faguer S, CKJ 2013

**APS**  
Bakhtar O Transplantation, 2014

**Gemcitabine**  
Starck M, BJH, 2013  
Al Ustwani, JGO, 2014

**HELLP syndrome**  
Fakhouri F, Blood 2010

**Cancer-associated TMA**  
Favre G, BJH, 2014

**SLE**  
El-Husseini, AJKD 2015
Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplantation-associated thrombotic microangiopathy

Sonata Jodele, Christoph Licht, Jens Goebel, Bradley P. Dixon, Kejian Zhang, Theru A. Sivakumaran, Stella M. Davies, Fred G. Pluthero, Lily Lu, and Benjamin L. Laskin

Table 2. Complement system analysis in patients with HSCT-TMA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Transplant type</th>
<th>C1r,C1s,C2,C4,SC5b-9</th>
<th>Recipient CFH-CFHR5 (MLPA)</th>
<th>Donor CFH-CFHR5 (MLPA)</th>
<th>CFH antibody (ELISA)</th>
<th>CFHR1 protein analysis (western blot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>autologous</td>
<td>normal alleles</td>
<td>del(CFH3-CFHR1)</td>
<td>n/a</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>2</td>
<td>autologous</td>
<td>normal alleles</td>
<td>del(CFH3-CFHR1)</td>
<td>n/a</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>3</td>
<td>autologous</td>
<td>normal alleles</td>
<td>del(CFH4-CFHR1)</td>
<td>n/a</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>4</td>
<td>allogeneic</td>
<td>normal alleles</td>
<td>del(CFH4-CFHR1)</td>
<td>normal allele</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>5</td>
<td>allogeneic</td>
<td>normal alleles</td>
<td>del(CFH3-CFHR1)</td>
<td>*del(CFH3-CFHR1)</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>6</td>
<td>allogeneic</td>
<td>normal alleles</td>
<td>normal allele</td>
<td>normal allele</td>
<td>present</td>
<td>present</td>
</tr>
</tbody>
</table>


Laskin, Transplantation, 2013
Laskin, Transplantation, 2013

Table 2. Complement system analysis in patients with HSCT-TMA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Transplant type</th>
<th>CFI,CFH,MCP,CFB,CFR5 (MLPA)</th>
<th>Recipient CFH-CFHR5 (MLPA)</th>
<th>Donor CFH-CFHR5 (MLPA)</th>
<th>CFH antibody</th>
<th>CFHR1 protein analysis (western blot)</th>
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<tr>
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<td>autologous</td>
<td>normal alleles</td>
<td>*del(CFH3-CFHR1)</td>
<td>n/a</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>3</td>
<td>autologous</td>
<td>normal alleles</td>
<td>*del(CFH1-CFHR4)</td>
<td>n/a</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>4</td>
<td>allogenic</td>
<td>normal alleles</td>
<td>*del(CFH3-CFHR1)</td>
<td>normal allele</td>
<td>present</td>
<td>present</td>
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<td>5</td>
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<td>*del(CFH3-CFHR1)</td>
<td>normal allele</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>6</td>
<td>allogenic</td>
<td>normal alleles</td>
<td>normal allele</td>
<td>normal allele</td>
<td>present</td>
<td>present</td>
</tr>
</tbody>
</table>

Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy.
Jodele S, Biol Blood Marrow Transplant, 2014

Successful use of eculizumab in a patient with post-transplant thrombotic microangiopathy.
Peffault de Latour R, Br J Haematol 2013
Eculizumab and typical HUS

Complement Blockade in Severe STEC-HUS.
Lapeyraque AL NEJM 2011
**Eculizumab and typical HUS**

**Complement Blockade in Severe STEC-HUS.**

Lapeyraque AL NEJM 2011

---

**Figure 1. Response to Eculizumab Therapy in Three Children with STEC-HUS and Progressive Cerebral Nervous System Involvement.**

Shown are data indicating rapid clinical improvement after the administration of intravenous C5 antibody, eculizumab in three children with the hemorrhagic-uricemic syndrome associated with infection with Shiga toxin-producing Escherichia coli (STEC-HUS), resulting in cerebral nervous system involvement (as shown in Patient 1 in Panel A). In all three children, there was rapid normalization in plasma creatinine levels and in radial artery oximetry, as well as in plasma creatinine and factor D complement levels.

---

**Conclusions**

Enterohaemorrhagic *E. coli* induced haemolytic uraemic syndrome is a severe self limiting acute condition. Our findings question the benefit of eculizumab and of plasmapheresis with or without glucocorticoids. Patients with established haemolytic uraemic syndrome seemed to benefit from antibiotic treatment and this should be investigated in a controlled trial.

---

**Validation of treatment strategies for enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome: case-control study**

DGKE disruption ditches complement and drives p38 signaling

K. Vinod Vijayan  BAYLOR COLLEGE OF MEDICINE; MICHAEL E. DEBAKEY VETERANS AFFAIRS MEDICAL CENTER

[Diagram showing signaling pathways involving DGKE, p38, Apoptosis, Migration, and Angiogenesis]
Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome

Loss of DGKε induces endothelial cell activation and death independently of complement activation

Sarah Bruneau,1 Mélanie Néel,1 Lubka T. Roumenina,2,3,4 Marie Frimat,2,5 Lætitia Laurent,1 Véronique Frémeaux-Bacchi,2,6 and Fadi Fakhouri1

A

% Inhibition

DGKε mRNA expression

Control siRNA
siRNA 10nM
siRNA 20nM

HUVEC
HMEC

B

DGKε

β-Actin

Control siRNA
siRNA 10nM
siRNA 20nM

HUVEC
HMEC

C

Tissue Factor secretion

Group

48 hrs
72 hrs

Unstained
Control siRNA
siRNA 10nM
siRNA 20nM

HMEC

D

TF expression

MFI (unit change)

Control siRNA
siRNA 10nM
siRNA 20nM

HUVEC
HMEC

E-selectin

ICAM-1

Control siRNA
siRNA 10nM
siRNA 20nM

HUVEC
HMEC

D

Control siRNA
DGKε siRNA

Number of adherent
plates (fold change)

Control siRNA
siRNA 10nM
siRNA 20nM

HUVEC
HMEC
Loss of DGKε induces endothelial cell activation and death independently of complement activation

Sarah Bruneau, Mélanie Néel, Lubka T. Roumenina, Marie Frimat, Lætitia Laurent, Véronique Frémeaux-Bacchi, and Fadi Fakhouri

A

B

C

A

B
Phenotypic Expansion of DGKE-Associated Diseases

Rik Westland,*† Monica Bodria,‡ Alba Carrea,† Sneh Lata,* Francesco Scolari,‖ Veronique Fremeaux-Bacchi,*** Vivette D’Agati,†† Richard P. Lifton,†‡ Ali G. Gharavi,* Gian Marco Ghiggeri,† and Simone Sanna-Cherchi*

Complement Mutations in Diacylglycerol Kinase-ε–Associated Atypical Hemolytic Uremic Syndrome

Daniel Sánchez Chinchilla,* Sheila Pinto,* Bernd Hoppe,* Marta Adraga,§ Laura Lopez,§ Maria Luisa Justa Roldan,§ Antonia Peña,* Magalía Lopez Trascasa,*** Pilar Sánchez-Corral,†*** and Santiago Rodríguez de Córdoba*†
Activation de la VAC persistante en rémission clinique?

« Pro »
- Ménigite (x5000)
- Perfusions
- Coût

« Con »
- Rechute
- IRA
- IRC
- Manifestations extra-rénales
For how long?

Age

Quality of renal recovery

COMPLEMENT GENETICS

Psychology patient/doctor

Pregnancy

Biomarkers?
The risk of relapse after eculizumab discontinuation appears to depend on the genetic background. 36 patients in the literature (native kidneys)

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Patients who discontinued N</th>
<th>Patients who relapsed after discontinuation N (%)</th>
<th>Mean duration of eculizumab treatment in relapsers months</th>
<th>Mean delay from eculizumab discontinuation to relapse months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>9 (2 on dialysis)</td>
<td>5* (55)</td>
<td>8 (5.5-14)</td>
<td>2.7 (0.9-6)</td>
</tr>
<tr>
<td>MCP</td>
<td>6</td>
<td>1 (16)</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>CFI</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>1 (on dialysis)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation identified</td>
<td>17 (4 on dialysis)</td>
<td>1* (6)</td>
<td>6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

7/36 (19.4%) relapsed after discontinuation. Treatment was reinitiated and outcome favourable in all.

* In 1 patient with CFH/CFHR1 hybrid and 1 with no mutation identified, both on dialysis, eculizumab was re-initiated because of significant hemolysis causing hyperkaliemia


Courtesy of Mrs Loirat
For how long?

PHRC: ECUSTOP
In all

- Eculizumab has transformed the outcome of aHUS.

- Optimal duration of treatment is unknown.

- Place of eculizumab in secondary HUS remains to be assessed.