aHUS
To stop or not to stop eculizumab?

Proposals issuing from the
April 26, 2013 meeting of the French Study
Group for aHUS and C3G

F. Fakhouri, C. Loirat and V. Fremeaux-Bacchi, February 1, 2014
Reason to question life-long eculizumab treatment

Nobody knows the new natural history of patients who have preserved renal function under eculizumab: what will be their course following eculizumab withdrawal?
Current proposals take into account

- Prognosis according to age at onset
- Phenotype-genotype correlations
- The risk of relapses according to age at onset, genetic background and time since onset
- The role of infections as triggers of relapses in children
- The risk of meningococcal infection under eculizumab
Prognosis of aHUS according to age at onset and genotype

French Cohort, Pre-eculizumab era
Renal outcome is better but mortality higher in children than in adults
French cohort, pre-eculizumab era, 214 patients

Number of aHUS patients at risk

<table>
<thead>
<tr>
<th></th>
<th>Pediatric onset (n=89)</th>
<th>Adult onset (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>89 34 17 13 6</td>
<td>125 18 7 2 0</td>
</tr>
</tbody>
</table>

Mortality: 8% in children, 2% in adults

End stage renal failure or death

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode</td>
<td>16%</td>
<td>46%</td>
</tr>
<tr>
<td>1 yr f-up</td>
<td>29%</td>
<td>56%</td>
</tr>
<tr>
<td>5 yrs f-up</td>
<td>36%</td>
<td>64%</td>
</tr>
</tbody>
</table>

39% of children and 80% of adults received plasma exchanges (PE)/plasma infusions (PI) at first episode

Fremeaux-Bacchi et al, CJASN 2013
Prognosis according to age at onset and genotype
French cohort, pre-eculizumab

• Whatever the age at onset, CFH-HUS have a catastrophic prognosis
• Prognosis of CFI-HUS and C3-HUS is slightly less severe, without significant differences between adults and children

Fremeaux-Bacchi et al, CJASN 2013
Prognosis according to age at onset and genotype

French cohort, pre-eculizumab

- In adults, prognosis of MCP-HUS and HUS with no mutation identified is as poor as that of CFH/CFI/C3-HUS
- In children, HUS with no mutation identified has a more favourable prognosis
- MCP-HUS with pediatric onset has the best prognosis (25% of ESRD at median follow-up 17.8 years)

Fremeaux-Bacchi et al, CJASN 2013
But all HUS are not complement-dependent...
The new gene: recessive *DGKE* mutations cause aHUS and appear to have a low risk of post-transplant recurrence

DGKE encodes diacylglycerol kinase ε (lipid kinases family) expressed in endothelium, platelets and podocytes

13 children with sporadic (6 pedigrees) or familial (3 pedigrees, 2–3 siblings) aHUS

- **Onset before 1 yr:** 13/13
- DGKE mutations explain 27% (13/49) of aHUS presenting in the first year of life
- Relapses during the 5 1st years
- HT, proteinuria ± NS, hematuria → CKD grade 4/5 between 20 and 25 yrs
- **Uncertain efficacy of eculizumab (7 cases)**
- **No post-transplant recurrence (3 cases)**

Lemaire, Fremeaux-Bacchi *et al.*
*Nature Genetics* 2013
The risk of relapses in patients surviving the first episode without ESRD

French cohort, pre-eculizumab
214 patients (89 children, 125 adults)

V. Fremeaux-Bacchi et al, CJASN 2013, modified: 5 children classified in the article as « no mutation identified » and 1 child as CFB mutation are now known to have DGKe mutation. Therefore the risk of relapses has been re-analysed to take into account this new group.
### aHUS is a relapsing disease

Among patients who had not died or reached ESRD at 1st episode, 43% (28/65) of children and 35% (23/66) of adults had relapses.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>All</th>
<th>CFH</th>
<th>CFI</th>
<th>MCP*</th>
<th>C3</th>
<th>DGKe</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>65</td>
<td>13</td>
<td>5</td>
<td>12</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Adults</td>
<td>66</td>
<td>19</td>
<td>8</td>
<td>11</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>21</td>
</tr>
</tbody>
</table>

* Relapses in MCP-HUS: 83% in children vs 33% in adults, p=0.03

Fremeaux-Bacchi et al, CJASN 2013; modified
The risk of relapse during the first year

Among patients who had not died or reached ESRD at 1st episode, 25% (16/65) of children and 29% (19/65 documented) of adults had relapses the 1st year.

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Adults</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

*Children: 13 CFH, 5 CFI, 12 MCP, 7 C3, 5 DGKe, 21 None

Adults: 19 CFH, 8 CFI, 11 MCP, 7 C3, 0 DGKe, 21 None

Fremeaux-Bacchi et al, CJASN 2013, modified
The risk of relapse after the first year

Among patients who had not died or reached ESRD at 1st episode, 47% (25/53) of children and 20% (11/55) of adults had relapses after the 1st year, p= 0.002

Fremeaux-Bacchi et al, CJASN 2013, modified

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>CFH</th>
<th>CFI</th>
<th>MCP</th>
<th>C3</th>
<th>DGKe</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>53</td>
<td>8</td>
<td>3</td>
<td>12</td>
<td>4</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Adults</td>
<td>55</td>
<td>16</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>
Among relapsers, the high risk period for relapse is mostly the first year

82% (19/23) of 1st relapses in adults and 57%(16/28) in children occurred during the 1st year, a high risk period except for MCP-HUS and C3-HUS in children

Fremeaux-Bacchi et al, CJASN 2013, modified
Among relapsers, the risk of 1st relapse after the 1st year is < 20%, except in children with MCP/C3/no mutation-HUS and adults with C3-HUS

13% (3/23) of first relapses in adults and 43% (12/28) in children occurred after the 1st yr.

Fremeaux-Bacchi et al, CJASN 2013, modified
The risk of invasive meningococcal infection is one of the reasons to question life-long maintenance of eculizumab
Invasive meningococcal infections (meningitis) in aHUS patients treated with eculizumab

**Continuous antibioprophylaxis obligatory in France**
- Oral methyl penicillin (full dose, twice daily) (resistance not exceptionnal)

**Invasive meningococcal infection reported in**

- **Two patients** (transplanted; CFH mutation; 17 and 19 y; vaccinated; no antibioprophylaxis) treated outside of protocol (out of approximately 65) (Davin, AJKD 2010 and Bouts, Pediatr Nephrol 2011; Struikik, AJT 2013)
- **Two patients in trial C10-004 (out of 100 patients treated within trials)** (Fakhouri et al, ASN, FR-OR057, Nov 8, 2013)
- **First case in France**, April 2013, Pau-Bordeaux: young woman; HUS on native kidneys; CFH mutation; vaccinated and on prophylactic methyl-penicilline (penicilline resistant meningococcus)
  → Favourable outcome in all

**Obligatory anti-meningococcal vaccine**
- Conjugate tetravalent vaccines against serogroups A, C, W135 and Y
- Anti-B vaccine (Bexsero) available in France since Dec 11, 2013 must now be associated

**Repeated information** to the patient, his family and family doctor
- **Information card**
Proposals for children (< 18years)
The specific problem of anti-CFH antibody-associated HUS
Favorable outcome if treated early
(PE+steroids+immunosuppressive trt)
French pediatric cases

Monitoring of anti-CFH Ab should
guide treatment tapering

Fremeaux-Bacchi et al, CJASN 2013

MCP vs anti CFH Ab (p=0.6)
CFH vs anti CFH Ab (p=0.02; OR : 3.7 [1.2 -11])
CFH vs MCP (p=0.002; OR : 5.8 [1.8 -18])

Dragon-Durey et al, JASN 2010

Number of aHUS patients
CFH 19 6 4 3 2 1
MCP 12 12 10 9 8 8
Anti CFH Ab 10 9 6 5 5 4

Overall Renal survival (%)
Time (months)

aHUS with anti-CFH Ab
Anti-CFH antibody-associated HUS
Benefit from early PE+ immunosuppression with subsequent maintenance immunosuppression

Sinha et al, KI 2013
Which treatment for aHUS with anti-CFH antibodies?

1\textsuperscript{st} episode of aHUS in a \textit{pre-adolescent / adolescent child}

- **Eculizumab** as first line treatment, within 24h after onset

Positive anti-CFH Ab

- **Without extra-renal manifestations**
  - Switch to PE + IV cyclophosphamide (rather than rituximab) + corticosteroids

- **With extra-renal manifestations**
  - Potential indication for PE + eculizumab + IV cyclophosphamide + corticosteroids
    - Stop PE when Ab titer < 500 -1000 AU/ml
    - Stop eculizumab after \(\approx\) 3 months of full (or partial but stabilized) renal recovery

Maintenance trt with MMF+ corticosteroids, guided by anti-CFH Ab titer
Criteria required for considering withdrawal of eculizumab in children
(anti-CFH antibody-HUS excluded)

Principle: Eculizumab withdrawal will not be considered in children who have not recovered normal GFR under eculizumab, to avoid any additional loss of GFR in case of relapse
Criteria required for considering eculizumab withdrawal in children

- **Clinical remission:** no manifestations of micro or macro-vascular TMA, such as
  - cerebro-vascular events or other neurologic manifestations
  - ischemic cardiac events or cardiomyopathy
  - peripheric/distal ischemic manifestations
  - pulmonary arterial hypertension
  - pancreatitis...

AND

- **Full hematologic remission:**
  - Hemoglobin $\geq$ 11g/dl
  - LDH $\leq$ ULN
  - Schizocytes$< 1\%$
  - Haptoglobin $\geq$ LLN
  - Plaquettes $\geq$150 000/mm3

AND

- **FULL renal recovery:**
  - eGFR $\geq$ 90 ml/min/1.73 m2
  - Normal U prot/creat ($\leq$ 0.02 g/mmol ou 0.20 g/g) or at least negative urine stick
  - Normal BP under $\leq$1 anti-HT drug
  - No microscopic hematuria ($< 10 000$ RBC/ml)
Genetics is essential for the decision of eculizumab withdrawal in children
Timing for eculizumab withdrawal in children treated for a first episode of aHUS on native kidneys

1. Isolated MCP mutation associated - HUS

First episode
Evolution generally favourable after each episode and low risk of ESRD despite relapses

Stop eculizumab after 3 months of full remission + full renal recovery under eculizumab

Early relapse (≤ 1 year after eculizumab withdrawal)
• Immediate reinitiation of eculizumab (delay < 24h),
• Investigate for immune deficiency

Stop eculizumab after 6 months of full remission + full renal recovery under eculizumab

Late relapse (> 1 year after eculizumab withdrawal)
• Immediate reinitiation of eculizumab (delay < 24h)

Stop eculizumab after 3 months of full remission + full renal recovery under eculizumab
Timing for eculizumab withdrawal in children treated for the first episode of aHUS on native kidneys

2. HUS other than MCP-HUS

**Mutation with high risk of ESRD in case of relapse**
- CFH mutation, CFH/CFHR1 recombination/hybrid CFH
- C3 or CFB gain of function mutation
- Combined mutations
- CFI mutation

Stop eculizumab
- Not before the end of 3rd year of life (3rd birthday)
  AND
- After 2 years of full remission and full renal recovery under eculizumab

**Other situations**
- Rare variant
- No mutation identified

Stop eculizumab
- After 1 year of full remission and full renal recovery under eculizumab
Eculizumab withdrawal in adults
Timing for eculizumab withdrawal in adults treated for the first episode of aHUS on native kidneys

Stop eculizumab
- After 1 year of full remission and full renal recovery under eculizumab or partial recovery with no TMA biological features and/or lesions on renal biopsy
Points common to adults and children
Biological monitoring after eculizumab withdrawal

**Which biological monitoring**
BCC, schizocytes, haptoglobin, LDH, creatinine
Education of the patient for urine dipstick for protein and hemoglobin (or urinary protein/creatinine ratio and RBC count on urine sample)

**Frequency after eculizumab withdrawal**
- 1/ week during the first month (+ urine dipstick 2/week)
- 1/ 2weeks from M2 to M6 (+ urine dipstick 2/week)
- 1/month after M6 (+ weekly urine dipstick)

**Intensified monitoring in case of infection, vaccination, surgery, traumatism :**
2/week 1st week, then 1/week x 3 weeks

**NB:** monitoring schedule to be potentially modified according to additional information about the delay of occurrence of relapses in patients who stopped treatment
Reasons to re-initiate eculizumab

- Complete triad of HUS
- Incomplete triad of HUS $\rightarrow$ Reinitiation within 12-24 h

- Signs of sub clinical TMA:
  - Normal Hb, platelet count and creatinine level but
  - LDH $>$ULN
  - Haptoglobin $<$ LLN
  - Isolated proteinuria / hematuria / HT $\rightarrow$ renal biopsy to confirm TMA lesions and eculizumab reinitiation
- Any extra-renal manifestation of TMA
  $\rightarrow$ Reinitiation after confirmation
Another circumstance for eculizumab withdrawal: resistance to treatment
Definition of resistance =
Symptoms/signs of ongoing TMA despite complement blockade

- Despite doses/intervals allowing complete and permanent complement blockade (monthly controls) as suggested by
  - Trough CH50 < 10% (according to technique)
  - Trough free eculizumab level >150ug/ml

- Ongoing TMA defined by
  - Persistence or relapse of hemolysis (LDH>ULN, Hb<10g/dl, hapto < LLN, ±schizo>1%)
  - and/or persistence or relapse of thrombocytopenia < 150.000/mm3
  - and/or persistence or appearance of proteinuria (U protein/creat >0.02-0.20 g/mm (mild-moderate) or ≥0.20 g/mm (important)) and/or hematuria >200 000 RBC/ml, and/or no improvement of GFR with active TMA lesions at renal biopsy (double contours ± arteriolar thrombi arteriolaires)

- A fortiori if DGKe mutation identified
Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome: A Report of 10 Cases

Ardissino, AJKD 2013

Table 1. Patients’ Baseline Characteristics and Biomarkers of TMA Activity Before Eculizumab Discontinuation and at Last Available Observation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at aHUS Onset (y)</th>
<th>Sex</th>
<th>Complement Abnormality</th>
<th>Response</th>
<th>Time Since Start of Eculizumab (mo)</th>
<th>Duration of Eculizumab Discontinuation (mo)</th>
<th>Scr (mg/dL)</th>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Platelet Count (×10⁹/µL)</th>
<th>LDH (IU/L)</th>
<th>Haptoglobin (mg/dL)</th>
<th>UPCR (mg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.3</td>
<td>M</td>
<td>CFH (p.Ser1191Leu)</td>
<td>Yes</td>
<td>31.0</td>
<td>1.5</td>
<td>0.92 (49)</td>
<td>0.80 (58)</td>
<td>334 290 367 206</td>
<td>97 103</td>
<td>0.67 0.17</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37.7</td>
<td>F</td>
<td>CFH (p.Arg1210Cys) + CFI (p.Asp519Asn) + THBD (p.Ala43Thr)</td>
<td>Yes</td>
<td>25.2</td>
<td>0.9</td>
<td>1.41 (44)</td>
<td>1.25 (51)</td>
<td>244 227 482 219</td>
<td>117 94</td>
<td>1.53 0.96</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>52.7</td>
<td>M</td>
<td>CFH (p.Ile140Thr)</td>
<td>No</td>
<td>24.8</td>
<td>22.7</td>
<td>1.03 (97)</td>
<td>1.00 (100)</td>
<td>180 256 467 371</td>
<td>312 252</td>
<td>NA 0.08</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>34.8</td>
<td>F</td>
<td>CFH (p.Gly269Ser)</td>
<td>No</td>
<td>21.5</td>
<td>10.1</td>
<td>2.72 (29)</td>
<td>2.54 (22)</td>
<td>261 286 406 403</td>
<td>98 88</td>
<td>1.38 0.70</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>M</td>
<td>CFH (p.Asp519Asn)</td>
<td>No</td>
<td>21.4</td>
<td>15.9</td>
<td>0.43 (132)</td>
<td>0.44 (117)</td>
<td>261 299 517 426</td>
<td>68 105</td>
<td>0.35 0.24</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.3</td>
<td>F</td>
<td>Homozygous deletion at CFHR3/R1 locus</td>
<td>No</td>
<td>19.9</td>
<td>6.5</td>
<td>0.29 (128)</td>
<td>0.27 (138)</td>
<td>447 390 688 654</td>
<td>91 60</td>
<td>3.46 2.32</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>19.4</td>
<td>M</td>
<td>Anti-CFH antibody (titer, 27 IU)</td>
<td>No</td>
<td>19.8</td>
<td>14.2</td>
<td>1.32 (72)</td>
<td>1.20 (79)</td>
<td>245 167 390 325</td>
<td>236 178</td>
<td>0.14 0.08</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5.4</td>
<td>F</td>
<td>MCP (p.Phe75Val)</td>
<td>No</td>
<td>14.0</td>
<td>13.5</td>
<td>1.28 (36)</td>
<td>0.52 (39)</td>
<td>300 420 682 423</td>
<td>46 78</td>
<td>3.21 0.20</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>13.3</td>
<td>M</td>
<td>Anti-CFH antibody (titer, 100 IU) + homozygous deletion at CFHR3/R1 locus</td>
<td>No</td>
<td>11.2</td>
<td>8.6</td>
<td>0.64 (110)</td>
<td>0.58 (122)</td>
<td>268 298 435 371</td>
<td>108 106</td>
<td>0.22 0.19</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10.9</td>
<td>F</td>
<td>CFH (p.Glu550His) + homozygous deletion at CFHR3/R1 locus + anti-CFH antibody (titer, 230 IU)</td>
<td>Yes</td>
<td>6.4</td>
<td>1.2</td>
<td>0.95 (73)</td>
<td>0.66 (105)</td>
<td>180 229 466 221</td>
<td>88 88</td>
<td>0.45 0.12</td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing time on and off eculizumab]
En France…

34 pts (E + Ad) : arrêt Ecu

5 rechutes (14%)

4 FH et 1 MCP