Issues in the treatment of aHUS

Plasma therapy fails to curb complement activation and EC damage and improve renal function.

Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS

Roxanne Cofield, Anjali Kulmeja, Krystin Bedard, Yan Yan, Angela P. Mickle, Masayo Ogawa, Camille L. Bocrostan and Susan J. Faab
Issues in the treatment of aHUS

Plasma therapy fails to curb complement activation and EC damage and improve renal function.

65% of patients were treated with plasma exchange / plasma infusion.

68% of patients were treated with plasma exchange / plasma infusion.
Issues in the treatment of aHUS

Eculizumab inhibits complement activation and EC damage and improves renal function. (prospective non-controlled trials)

Adults

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

French cohort: Fremeaux-Bacchi et al, CJASN 2013

C. Loirat
Ped Nephrol, 2015
Eculizumab inhibits complement activation and EC damage and improves renal function. (retrospective studies)

<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>
Issues in the treatment of aHUS

Why does a minority of patients not respond to Ecu?
How to monitor complement blockade (CH50, AP50, free vs total C5, EC tests)?
  sC5b-9 may remain detectable...
  Other therapeutic options?
  Prophylaxis?
Issues in the treatment of aHUS

What is the best strategy for aHUS due to anti-FH antibodies?

PE + Immunosuppressive therapies ± eculizumab (or vice-versa)?

Monitoring of anti-CFH Ab should guide treatment tapering

Sinha, KI 2013
Issues in the treatment of aHUS

What pathophysiological model apply to secondary HUS?

Initial insult
- drugs,
- radiation
- cancer,
- etc.

Eculizumab?

Complement activation = 2\textsuperscript{nd} amplifying hit?
Issues in the treatment of aHUS

For how long should we use eculizumab in aHUS patients?

Does chronic « clinically-relevant » complement activation occur in all aHUS patients?

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(Menne, ASN 2015)
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Can eculizumab be discontinued in some patients and how to select candidates for eculizumab withdrawal?

- Age
- Quality of renal recovery
- Duration of Ecu treatment
- Native kidneys vs renal graft
- Willingness of the patient (physician)
- Biomarkers C activation / EC damage
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Native kidneys vs renal graft
Willingness of the patient (physician)
Biomarkers C activation / EC damage
Complement genetics
Issues in the treatment of aHUS

For how long should we use eculizumab in aHUS patients?

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>Complement Abnormality‡</th>
<th>Time Since Start of Eculizumab (mo)</th>
<th>Duration of Eculizumab Discontinuation (mo)</th>
<th>Scr (eGFR)</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></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</td>
<td>87 103</td>
</tr>
<tr>
<td>2</td>
<td>37.7</td>
<td>F</td>
<td>CFH (p.Arg1210Cys) + CFI</td>
<td></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</td>
<td>84 219</td>
</tr>
<tr>
<td>3</td>
<td>52.7</td>
<td>M</td>
<td>CFI (p.Ile140Thr)</td>
<td></td>
<td>No</td>
<td>24.3</td>
<td>22.7</td>
<td>1.03 (97)</td>
<td>1.00 (100)</td>
<td>180 256</td>
<td>467 371</td>
</tr>
<tr>
<td>4</td>
<td>34.8</td>
<td>F</td>
<td>CFI (p.Gly269Ser)</td>
<td></td>
<td>No</td>
<td>21.5</td>
<td>10.1</td>
<td>2.72 (29)</td>
<td>2.54 (22)</td>
<td>281 286</td>
<td>406 403</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>M</td>
<td>CFI (p.Asp519Asn)</td>
<td></td>
<td>No</td>
<td>21.4</td>
<td>15.9</td>
<td>0.38 (132)</td>
<td>0.44 (117)</td>
<td>261 299</td>
<td>517 426</td>
</tr>
<tr>
<td>6</td>
<td>1.3</td>
<td>F</td>
<td>Homozygous deletion at CFHR3/R1 locus</td>
<td></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</td>
<td>688 654</td>
</tr>
<tr>
<td>7</td>
<td>19.1</td>
<td>M</td>
<td>Anti-CFH antibody (titer, 27 IU)</td>
<td></td>
<td>No</td>
<td>19.8</td>
<td>14.2</td>
<td>1.33 (72)</td>
<td>1.20 (79)</td>
<td>245 167</td>
<td>390 325</td>
</tr>
<tr>
<td>8</td>
<td>5.4</td>
<td>F</td>
<td>MCP (p.Phe175Val)</td>
<td></td>
<td>No</td>
<td>14.0</td>
<td>13.5</td>
<td>1.28 (36)</td>
<td>0.52 (69)</td>
<td>300 420</td>
<td>682 423</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></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</td>
<td>435 371</td>
</tr>
<tr>
<td>10</td>
<td>10.9</td>
<td>F</td>
<td>CFH (p.Glu950His) + homozygous deletion at CFHR3/R1 locus + anti-CFH antibody (titer, 230 IU)</td>
<td></td>
<td>Yes</td>
<td>6.4</td>
<td>1.2</td>
<td>0.95 (73)</td>
<td>0.66 (105)</td>
<td>180 239</td>
<td>466 221</td>
</tr>
</tbody>
</table>
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Can eculizumab be discontinued in some patients
and how to select candidates for eculizumab withdrawal?

When a relapse has occurred what is the optimal treatment strategy?
Issues in the treatment of aHUS

$n = 57$ aHUS pts + 71 RT

Renal transplantation in aHUS

Graft Survival

Le Quintrec M, AJT 2013

Prophylactic use of eculizumab in high-risk patients for aHUS recurrence.
Combined liver-renal transplantation in selected patients?
Issues in the treatment of aHUS

n = 57 aHUS pts + 71 RT

Renal transplantation in aHUS

Prophylactic use of eculizumab in high-risk patients for aHUS recurrence.

Combined liver-renal transplantation in selected patients?

Optimal duration of treatment in RT patients with aHUS?