The new generation of complement inhibitors and implications for clinical practice and vaccination policy

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Activation of the complement

- Humoral innate immunity system
- Acute-phase proteins
- 19 plasma and at least 9 membrane proteins

Harris et al., Molecular Immunology 102 (2018) 89–119
Complement pathophysiology

AD, Alzheimer’s disease
AMD, Age-related macular degeneration
DAMP, damage-associated molecular pattern;
DDD, dense deposit disease;
PAMP, pathogen-associated molecular pattern;
PMN, polymorphonuclear cell;
PNH, paroxysmal nocturnal hemoglobinuria;
SLE, systemic lupus erythematosus.
Pipeline for anti-complement drugs in the kidney, eye and vasculature

Half-life of ravulizumab is 4 times longer than that of eculizumab
(Lee et al., Blood, 2016)
**Complement inhibition and hemolysis in PNH**

- **No Complement activation**
  - CD55
  - CD59
  - No lysis

- **Complement Activation on PNH RBC**
  - Lysis of PNH RBC
    - Insertion of C5b-9 MAC (intravascular hemolysis)
    - Opsonization with C3b (extravascular hemolysis)

- **Eculizumab Complement Inhibition (C5 inhibition) on PNH RBC**
  - Lysis of PNH RBC is still occurring
    - Opsonization with C3b (extravascular hemolysis)

- **Compstatin Complement Inhibition (inhibition of C3b deposition) on PNH RBC**
  - Impact on both pathways
Risk groups for IMD

Medical reasons

- Close contacts of patients with IMD;
  - Subjects with a terminal complement deficiency or who are receiving anti-C5 treatment (and other future anti-complement treatment)
  - Subjects with other complement deficiencies (properdin Factor D)
- Subjects with anatomical or functional asplenia;
  - Subjects who received a hematopoietic stem cell transplantation
- HIV
- Association with viral infection (flu)

Occupational/societal reasons
Travellers, pilgrims, mass gathering events, military, laboratory staff working on meningococci, MSM, Students

Epidemic Situations
Complement and IMD

Inherited and drug induced complement deficiencies.


- 7/22 (32%) patients with NG IMD had complement deficiency or abnormal complement testing results (McNamara *et al.*, *Open Forum Infect Dis* 6, 2019).

- Among 160 patients with complete TPD; 56 patients (39%) showed confirmed IMD (France 1999-2015) (Rosain *et al.*, *J. Infect Dis* 2017).

## Complement deficiencies and IMD: Isolates


<table>
<thead>
<tr>
<th>Type of deficiency</th>
<th>N° of isolates/episodes (patients)</th>
<th>Isolates (n)</th>
<th>Fatal cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPD</td>
<td>63 (59)</td>
<td>B(19); C(2); <strong>Y(29)</strong>; W(9); E(4); <strong>NG(1)</strong></td>
<td>1</td>
</tr>
<tr>
<td>Factor D</td>
<td>1 (1)</td>
<td>B (1)</td>
<td>0</td>
</tr>
<tr>
<td>Properdin</td>
<td>1 (1)</td>
<td>Y (1)</td>
<td>1</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>3 (3)</td>
<td>Y(2); C(1)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Ladhani et al., BMC Infect Dis 2019: England 2008-2017**

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<tr>
<th>Type of deficiency</th>
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<th>Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited</td>
<td>11(8)</td>
<td>B(3); <strong>Y(7)</strong>; <strong>NG(1)</strong></td>
</tr>
<tr>
<td>Eculizumab</td>
<td>9 (8)</td>
<td>B(3+3NG); <strong>Y(1)</strong>; W(1); E(1)</td>
</tr>
</tbody>
</table>

- Heterogeneous isolates
- Frequent Y, E and NG isolates
- Only 21% belonging hyper-invasive CC (France)
Coverage of serogroup B and E isolates of the TPD patients by the 4CMenB vaccine

Data NRC, Institut Pasteur
Immunogenicity of MCC in a patient with aHUS on eculizumab therapy

A four-yr-old boy presented with aHUS

- TCC concentration reflects the ability to activate the complement system
- But SBA response seems to be impaired under treatment

Zlamy et al., Pediatr Transplantation 2012:
Penicillin-resistant case of IMD in patient on Eculizumab therapy

- Case of IMD due to a vaccine-preventable and penicillin-resistant strain in a fully immunised young adult (22 years) on long-term complement inhibitor therapy and daily penicillin chemoprophylaxis.

- First case of meningococcal group B vaccine failure in a young adult receiving Eculizumab for aHUS.

- Developed IMD due to capsular group B 4 months after receiving 2 doses of 4CMenB vaccine while on oral penicillin prophylaxis.

- Strain ST-162 (pathogenic potential).

- Capsular gene SiaDb interrupted by an insertion sequence.

- PenA allele contained 3 mutations associated with reduced penicillin sensitivity.

- PenA allele previously associated with *N. gonorrhoeae*.

- Strain confirmed covered by 4CMenB by MATS by NHBA antigen.

Courtesy from Prof R. Borrow

<table>
<thead>
<tr>
<th>EPIDEMIOLOGICAL YEAR</th>
<th>% OF ISOLATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010/11 (N=513)</td>
<td>66.67</td>
</tr>
<tr>
<td>2011/12 (N=408)</td>
<td>68.63</td>
</tr>
<tr>
<td>2012/13 (N=456)</td>
<td>60.96</td>
</tr>
<tr>
<td>2013/14 (N=404)</td>
<td>61.14</td>
</tr>
<tr>
<td>2014/15 (N=513)</td>
<td>68.62</td>
</tr>
<tr>
<td>2015/16 (N=523)</td>
<td>52.01</td>
</tr>
<tr>
<td>2016/17 (N=505)</td>
<td>67.13</td>
</tr>
<tr>
<td>2017/18 (N=368)</td>
<td>65.49</td>
</tr>
</tbody>
</table>

Susceptible (≤0.06 mg/L), Intermediate Resistance (0.06 mg/L < MIC ≤ 0.25 mg/L), Resistant (>0.25 mg/L)

Courtesy from Prof R. Borrow. PHE unpublished data.
Susceptibility to penicillin G

Data NRC, MK Taha, Institut Pasteur, Unpublished data
Penicillin is still effective against intermediate (resistant) isolates (mouse model)

Mice infected i.p. with isogenic susceptible or intermediate isolates (MIC 0.5 mg/L)

Conclusions (1)

- Increasing evidence of association of complement activation and degenerative diseases
- Anti-complement treatment may be benefic
- Complement deficiencies can be associated with increase susceptibility to IMD.
- Serogroup Y isolates predominate but NG can be important under anti-complement treatment
- Explore complement systematically when IMD is provoked with non hyperinvasive isolates.
- Explore complement systematically if IMD with vaccine preventable serogroup in vaccinated patients.
- If an inherited complement deficiency confirmed in the patient then explore the members of the family.
- Exploration of not only the determination of the CH50 activity but also the alternative pathway.
Conclusions (2)

• Vaccination of subjects with complement deficiencies (inherited and acquired) against ACWY and B

• Vaccination in not enough. Antibiotic treatment is required (High dose penicillin V ≥ 250 000 IU/Kg/day).

• Rescue antibiotics (i.e. self-treatment with a treatment course of amoxicillin (+ penicillin), ciprofloxacin or other antibiotics to be defined when unwell)?

• Vaccination of household contacts of subjects with complement deficiencies (cocooning strategy).