C3 Glomerulopathy

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MPGN: the old classification...

**MPGN Type I**
*Subendothelial deposits*
West et al, J Pediatr 1965

**MPGN Type II / DDD**
*Intramembranous deposits*

**MPGN Type III**
*Subendothelial and subepithelial deposits*
Burkholder et al, Am J Pathol 1969
Anders et al, Virchows Arch A Pathol Anat Histol 1997
Strife et al, Clin Nephrol 1984
19 patients with unusual glomerulonephritis and:
- C3NeF positivity (7), CFH (3), CFI (2) or MCP (1) mutations
- absence of dense intramembranous deposits (no DDD)
- overt mesangial and epimembranous C3 deposits
- no Ig deposition

→ **C3GN**
Complement AP dysregulation in kidney diseases

- **DDD/C3GN**
- **aHUS**
- **C3 Glomerulopathy**
The distinction C3GN/DDD requires electron microscopy

Walker PD et al, Modern Pathol 2007

• Proteomic profile of microdissected glomeruli: C3, C4, C5, C6, C7, C8, CFHR1, CFHR5....

• Very similar profile between DDD and C3GN

Sethi et al KI 2009; Sethi et al CJASN 2011
Renal biopsy in C3G

Pickering et al, KI 2013: C3 at least 2-fold brighter than other IF
Mesangial proliferative GN and MPGN represent a continuum
2012: new classification of MPGN: IC-MPGN vs C3G

Proliferative glomerulonephritis

Positive Igs +/- C3

- Ig-mediated
  - Monoclonal gammopathies
  - Dysproteinemia

- Autoimmune diseases

- Infections

Negative Igs + C3

- Complement-mediated

  - C3 Glomerulopathies
    - DDD
    - C3GN

Sethi S and Fervenza FC, Semin Nephrol 2011
Sethi S and Fervenza FC, NEJM 2012
Different alternative pathway alterations lead to C3 glomerulopathies

C3 glomerulopathies

modified from Sethi S, Fervenza FC NEJM 2012
Extrarenal features

Partial lipodystrophy

Macula

Drusen

Lipids & proteins
C3G: clinical presentation is heterogenous

- Post-infectious glomerulonephritis with low C3
C3G presenting as acute PIGN

- Post-infectious glomerulonephritis with
  1) low C3 that persists > 12 weeks or with
  2) recurrent macrohematuria

<table>
<thead>
<tr>
<th>Patient</th>
<th>CFH</th>
<th>CFHR5</th>
<th>FH antibodies</th>
<th>Hemolytic assay</th>
<th>APFA</th>
<th>C3NeF</th>
<th>sMAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c.2171delC, p.Thr724delX, 72S</td>
<td>No mutations</td>
<td>Negative</td>
<td>ND</td>
<td>ND</td>
<td>Negative</td>
<td>0.24 mg/l</td>
</tr>
<tr>
<td>2</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal 63% Abnormal</td>
<td>Negative</td>
<td>0.21 mg/l</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>1% Normal 63% Abnormal</td>
<td>Positive (C3CSAP*)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal 1% Abnormal</td>
<td>Positive (IFE)</td>
<td>1.23 mg/l</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>12% Abnormal 34% Abnormal</td>
<td>Positive (IFE)</td>
<td>0.48 mg/l</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal 1% Abnormal</td>
<td>Positive (both assays)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>c.3350A&gt;G, p.Asn1117Ser</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal 90% Abnormal</td>
<td>Negative</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal 123%</td>
<td>Negative</td>
<td>0.13 mg/l</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>9% Abnormal 77%</td>
<td>Positive (both assays)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>c.1699A&gt;G, p.Arg567Gly</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal 0% Abnormal</td>
<td>Positive (both assays)</td>
<td>2.03 mg/l</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal 130%</td>
<td>Positive (C3CSAP)</td>
<td>0.21 mg/l</td>
<td></td>
</tr>
</tbody>
</table>

Sethi et al, KI 2012
Atypical PIGN is a form of C3G

<table>
<thead>
<tr>
<th>Light microscopy</th>
<th>Immunofluorescence</th>
<th>Electron microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diff. prol.</strong></td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Mes. prol.</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>MPGN</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Crescentic</strong></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

| **C3 capill.**    | +++ | +++ | +++ |
| **C3 mesang.**    | +++ | +++ | +++ |
| **IgG**           | ++  | +  | +/- |
| **Humps**         | +++ | +++ | +  |
| **Mesangial**     | +/- | ++  | +++ |
| **Sub-endoth.**   | +/- | ++  | +++ |
C3G: clinical presentation is heterogenous

- Post-infectious glomerulonephritis with low C3

- Infection triggering macrohematuria, as in IgA nephropathy
CFHR nephropathy: C3G presenting as “IgA nephropathy”

- Infection-triggered macrohematuria, proteinuria

Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis

Gale et al, Lancet 2010
C3G: clinical presentation is heterogenous

• Post-infectious glomerulonephritis with low C3

• Infection triggering macrohematuria, as in IgA nephropathy

• Nephrotic syndrome
C3G: clinical presentation is heterogenous

- Post-infectious glomerulonephritis with low C3
- Infection triggering macrohematuria, as in IgA nephropathy
- Nephrotic syndrome
- Accidental finding of non-nephrotic proteinuria, microhematuria
## C3G: OPBG experience on 32 pediatric patients

<table>
<thead>
<tr>
<th>Clinical presentation (number of patients)</th>
<th>Urine</th>
<th>Biopsy</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M.E.</td>
<td>C3GN</td>
<td>DDD</td>
<td>None</td>
</tr>
<tr>
<td>Acute GN (13)</td>
<td>100%</td>
<td>92%</td>
<td>8%</td>
<td>31%</td>
</tr>
<tr>
<td>Nephrotic syndr. (11)</td>
<td>18%</td>
<td>91%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Random urine (8)</td>
<td>0%</td>
<td>50%</td>
<td>50%</td>
<td>13%</td>
</tr>
</tbody>
</table>
C3G: clinical presentation is heterogeneous

- Post-infectious glomerulonephritis with low C3
- Infection triggering macrohematuria, as in IgA nephropathy
- Nephrotic syndrome
- Accidental finding of non-nephrotic proteinuria, microhematuria
- Atypical
INITIAL PRESENTATION: aHUS

A 5-year old child was transferred in May 2014 from the Cosenza Pediatric Department with HUS, requiring hemodialysis.

UPON ARRIVAL

- Stool culture and serum antibodies were negative for VTEC
- ADAMTS13 levels were slightly reduced (40%)

1) A full workup of complement mutations was performed
2) Therapy with eculizumab was started

Following start of eculizumab, platelets rapidly increased and after 10 days hemodialysis was discontinued.

However, renal function remained abnormal with proteinuria in the nephrotic range and persistently low circulating C3.

Therefore, a renal biopsy was performed, which showed:
IgG C3

Courtesy of Dr F. Diomedi-Camassei
Clinical, histological and molecular overlaps of C3G

C3 glomerulopathies

Endocapillary
Intramembranous
Membrano or mesangioprolif.

PIGN
Atypical PIGN
DDD/C3GN
CFHR GN
IgAN

Predominant > 2-fold C3 deposition

Adapted from Zipfel et al, Molecular Immunology (2015)
New classification of MPGN: does the C3 predominance criterion really capture all patients?

Proliferative glomerulonephritis

- Positive Igs +/- C3
  - Ig-mediated
    - Monoclonal gammopathies
    - Dysproteinemia
    - Autoimmune diseases
    - Infections
      - DDD
      - C3GN
  - Complement-mediated
    - C3 Glomerulopathies

2012: IC-MPGN can also be secondary to dysregulation of the complement alternative pathway: C3Nef

Table 3 | Complement component analysis and immunofluorescence study of membranoproliferative glomerulonephritis type I cases with positive C3 nephritic factor

<table>
<thead>
<tr>
<th>Patient</th>
<th>C3 (660 to 1250 mg/l)</th>
<th>C4 (90 to 380 mg/l)</th>
<th>CFB (90 to 320 mg/l)</th>
<th>Histology</th>
<th>Immunofluorescence study</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>537b</td>
<td>160</td>
<td>83</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
</tr>
<tr>
<td>26</td>
<td>512</td>
<td>127</td>
<td>50</td>
<td>MPGN I</td>
<td>IgG, IgM, IgA, C3</td>
</tr>
<tr>
<td>27</td>
<td>183</td>
<td>178</td>
<td>225</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
<tr>
<td>28</td>
<td>701</td>
<td>233</td>
<td>96</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
<tr>
<td>29</td>
<td>87</td>
<td>202</td>
<td>51</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
</tr>
<tr>
<td>30</td>
<td>847</td>
<td>222</td>
<td>71</td>
<td>MPGN I</td>
<td>IgG, IgM, C3, C1q</td>
</tr>
<tr>
<td>31</td>
<td>48</td>
<td>126</td>
<td>89</td>
<td>MPGN I</td>
<td>IgG, IgA, C3</td>
</tr>
<tr>
<td>32</td>
<td>87</td>
<td>309</td>
<td>92</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
</tr>
<tr>
<td>33</td>
<td>293</td>
<td>209</td>
<td>100</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
</tr>
<tr>
<td>34</td>
<td>180</td>
<td>248</td>
<td>123</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
</tr>
<tr>
<td>35</td>
<td>193</td>
<td>95</td>
<td>126</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
<tr>
<td>36</td>
<td>275</td>
<td>225</td>
<td>159</td>
<td>MPGN I</td>
<td>IgG, IgM, C3, C1q</td>
</tr>
<tr>
<td>37</td>
<td>1110</td>
<td>162</td>
<td>186</td>
<td>MPGN I</td>
<td>NDc</td>
</tr>
<tr>
<td>38</td>
<td>475</td>
<td>175</td>
<td>155</td>
<td>MPGN I</td>
<td>IgG, IgA, C3</td>
</tr>
<tr>
<td>39</td>
<td>741</td>
<td>169</td>
<td>82</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
<tr>
<td>40</td>
<td>875</td>
<td>273</td>
<td>124</td>
<td>MPGN I</td>
<td>IgG, C3, C1q</td>
</tr>
<tr>
<td>41</td>
<td>135</td>
<td>182</td>
<td>130</td>
<td>MPGN I</td>
<td>IgG, IgA, IgM, C3</td>
</tr>
<tr>
<td>42</td>
<td>129</td>
<td>227</td>
<td>64</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
</tbody>
</table>

Abbreviations: CFB, complement factor B; Ig, immunoglobulin; MPGN I, membranoproliferative glomerulonephritis type I; ND, not done.

aLaboratory reference values are indicated in brackets.
bRare variant CFI IVS 12+5 associated.
cBiopsy performed in 1974: lobular MPGN I, no immunofluorescence study available. Cases with genetic abnormality are presented in Table 2.
A substantial percentage of patients with idiopathic IC-MPGN has complement AP dysregulation

The value of repeat biopsies: IC-MPGN to C3G

First biopsy

-  C1q
-  C3
-  IgG
-  IgM

Second biopsy

-  C1q
-  C3
-  IgG
-  IgM

Positive C3Nef
MCP mutation
Elevated C5b9
Persistent low C3

Courtesy of Dr F. Diomedi-Camassei
The value of repeat biopsies: C3G to IC-MPGN

First biopsy

Second biopsy

Positive C3Nef
No mutation
Normal C5b9
Persistent low C3

Courtesy of Dr. F. Diomedi-Camassei
C3 glomerulopathies

- Endocapillary
- Intramembranous
- Membrano or mesangioprolif.

PIGN
- Atypical PIGN
- DDD/C3GN
- IC-MPGN
- CFHR GN
- IgAN

C3 deposition often predominant, not exclusive

Adapted from Zipfel et al, Molecular Immunology 2015
Clinical presentation: extremely heterogenous

Histology:
LM: extremely heterogenous
IF: variable, C3 predominance very useful but co-existence of Igs and also C1q does not exclude complement AP dysregulation
EM: with intramembranous highly electron-dense deposits diagnostic

Serology:
Circulating low C3 with normal C4 very useful though not always present

GENETIC AND SEROLOGICAL PHENOTYPING IS ESSENTIAL!
### C3G/IC-MPGN: serological and genetic screening of the AP of complement

<table>
<thead>
<tr>
<th>Circulating factors</th>
<th>FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibodies</td>
<td>C3Nef</td>
</tr>
<tr>
<td>Genetic</td>
<td>Factor H</td>
</tr>
<tr>
<td></td>
<td>Factor I</td>
</tr>
<tr>
<td></td>
<td>MCP (CD46)</td>
</tr>
<tr>
<td></td>
<td>THBD</td>
</tr>
<tr>
<td></td>
<td>C3</td>
</tr>
<tr>
<td></td>
<td>Factor B</td>
</tr>
<tr>
<td></td>
<td>CFHR genes</td>
</tr>
</tbody>
</table>
Circulating C3 and C5b-9 according to renal histology

C3 convertase dysregulation:

DDD > C3GN

C5 convertase dysregulation:

C3GN > DDD

Servais et al, Kidney Int 2012

Zhang et al, CJASN 2014
Unbiased cluster analysis of 34 genetic, serologic, histologic and clinical features led to the identification of 4 groups with common features, distinct underlying mechanisms and different prognoses.

**Group 1** IF: predom. C3

**Elevated C5b9**

**Group 2** IF: C3, IgG, C1q

**Low C3 and frequent mutations in AP genes or C3Nef pos (fluid phase AP dysregulation)**

**Group 3** EM: DD

**Normal C5b9**

**Group 4** IF: predom. C3

**Normal C5b9**

**Late onset, marked sclerosis, poor outcome**

Normal C3 and infrequent mutations in AP genes or C3Nef (solid phase or low-grade continuous fluid phase AP dysregulation)

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Iatropoulos, Daina et al, JASN 2017
**Table 1 | Clinical and biological data according to histological type**

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>MPGN 1</th>
<th>DDD</th>
<th>GNC3</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>134</td>
<td>49</td>
<td>29</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td></td>
<td>81/53</td>
<td>32/17</td>
<td>17/12</td>
<td>33/24</td>
</tr>
<tr>
<td><strong>Children’s/adults</strong></td>
<td>52/82</td>
<td>21/28</td>
<td>17/12</td>
<td>14/42</td>
<td>58.8%</td>
</tr>
<tr>
<td><strong>Age at diagnosis (years)</strong></td>
<td>24.3 ± 18.6</td>
<td>20.7 ± 16.8</td>
<td>18.9 ± 17.7</td>
<td>30.3 ± 19.3</td>
<td>&lt;0.05&lt;sup&gt;a&lt;/sup&gt; and &lt;0.01&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Proteinuria (g/day)</strong></td>
<td>4.9 ± 4.1</td>
<td>6.9 ± 4.4</td>
<td>5.6 ± 4.5</td>
<td>3.6 ± 3.3</td>
<td>&lt;0.05&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Nephrotic syndrome</strong></td>
<td>58 (41.1%)</td>
<td>32 (65.3%)</td>
<td>11 (37.9%)</td>
<td>15 (26.8%)</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt; and 0.02&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Microhematuria</strong></td>
<td>83 (58.8%)</td>
<td>25 (51.0%)</td>
<td>22 (75.8%)</td>
<td>36 (64.3%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HBP</strong></td>
<td>43 (30.3%)</td>
<td>16 (32.6%)</td>
<td>6 (20.7%)</td>
<td>21 (37.5%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>eGFR (ml/min per 1.73 m²)</strong></td>
<td>69.3 ± 36.6</td>
<td>73.7 ± 33.7</td>
<td>75.5 ± 38.8</td>
<td>65.9 ± 37.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>ACE inhibitor/ARB treatment</strong></td>
<td>64 (45.4%)</td>
<td>27 (55.1%)</td>
<td>10 (34.5%)</td>
<td>27 (48.2%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Immunosuppressive treatment</strong></td>
<td>61 (43.2%)</td>
<td>28 (57.1%)</td>
<td>14 (46.3%)</td>
<td>19 (33.9%)</td>
<td>0.02&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Follow-up (years)</strong></td>
<td>11.2 ± 11.2</td>
<td>11.7 ± 12.0</td>
<td>12.0 ± 12.1</td>
<td>10.2 ± 10.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

**At last follow-up**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR (ml/min per 1.73 m²)</strong></td>
<td>50.4 ± 39.5</td>
<td>47.7 ± 40.3</td>
<td>53.8 ± 40.3</td>
<td>50.9 ± 37.1</td>
</tr>
<tr>
<td><strong>Proteinuria (g/day)</strong></td>
<td>2.2 ± 2.7</td>
<td>2.4 ± 3.5</td>
<td>1.4 ± 1.6</td>
<td>2.1 ± 2.4</td>
</tr>
<tr>
<td><strong>Nephrotic syndrome</strong></td>
<td>19 (14.1%)</td>
<td>8 (16.3%)</td>
<td>2 (6.9%)</td>
<td>9 (16.1%)</td>
</tr>
<tr>
<td><strong>Duration of evolution until ESRD</strong></td>
<td>10.3 ± 10.2</td>
<td>10.1 ± 9.8</td>
<td>9.8 ± 11.6</td>
<td>10.8 ± 10.0</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>49 (36.6%)</td>
<td>20 (40.8%)</td>
<td>12 (41.4%)</td>
<td>17 (30.3%)</td>
</tr>
<tr>
<td><strong>Age at dialysis (years)</strong></td>
<td>35.6 ± 17.6</td>
<td>30.3 ± 17.2</td>
<td>36.9 ± 18.1</td>
<td>40.8 ± 16.9</td>
</tr>
<tr>
<td><strong>Recall transplantation</strong></td>
<td>35 (26.1%)</td>
<td>14 (28.6%)</td>
<td>11 (37.9%)</td>
<td>10 (17.8%)</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>18 (51.4%)</td>
<td>2 (14.3%)</td>
<td>3 (27.3%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td><strong>Thrombotic microangiopathy</strong></td>
<td>6 (17.1%)</td>
<td>2 (14.3%)</td>
<td>1 (7.1%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td><strong>Vascular rejection</strong></td>
<td>2 (5.8%)</td>
<td>1 (7.1%)</td>
<td>0 (0%)</td>
<td>1 (10.0%)</td>
</tr>
</tbody>
</table>

Servais et al, KI 2012
Risk factors of poor long-term outcome in C3G

Multivariate analysis of the association of long-term renal outcome with clinical, laboratory and genetic features.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR</th>
<th>HR 95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of mutations or C3NeFs</td>
<td>7.1</td>
<td>1.9–26.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Sclerotic glomeruli (% of glomeruli)</td>
<td>69.3</td>
<td>3.1–1553</td>
<td>0.008</td>
</tr>
<tr>
<td>Crescents (% of glomeruli)</td>
<td>39.7</td>
<td>3.3–481</td>
<td>0.004</td>
</tr>
<tr>
<td>Nephrotic syndrome at onset</td>
<td>10.9</td>
<td>2.5–47</td>
<td>0.002</td>
</tr>
</tbody>
</table>

HR: hazard ratio calculated by Multivariate Cox proportional-Hazards analysis. CI: confidence Interval. nc: not calculable. Nephrotic syndrome was defined as: 24-h proteinuria exceeding 3.5 g in adults or 40 mg/h/m² in children together with albuminemia ≤3 g/dL. Intensified immunosuppression was also included in multivariate Cox Regression analysis but was not significantly associated with progress to ESRD (HR = 3.9, 95%CI 0.65–23.9, p = 0.138).
How to treat C3G?

Inflammation!
Treatment of C3G: mycophenolate

Effectiveness of mycophenolate mofetil in C3 glomerulonephritis

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Figure 1: Renal survival (defined by a status free of end-stage renal disease) in patients treated with MMF (MMF-IST), other IST (other-IST), and no IST (non-IST). ESRD, end-stage renal disease; IST, immunosuppressive treatments; MMF, mycophenolate mofetil.

Rabasco et al et al KI 2015
Goodship et al. KI 2017

Treatment of C3G: KDIGO guidelines

All patients:
optimal blood pressure (ACEi, ARB), diet and lipid control

Moderate disease (proteinuria > 500 mg/24h, moderate inflammation on renal biopsy) :
prednisone, MMF

Severe disease (proteinuria >2000 mg/24h, severe inflammation with marked endo and
eextracapillary proliferation, increase in serum creatinine):
• i.v. methylprednisolone + anti-cellular immunosuppressants (limited success)
• Evidence insufficient to recommend eculizumab as first-line agent

Goodship et al. KI 2017
Complement-targeting therapies: anti-C5 blocks the terminal complement pathway

Rother et al. Nature Biotechnology 2007
ATTENTION:

- not all patients respond so well
- it may work better in those with elevated sC5b9
- expensive and there is a risk of meningococcal infection
Complement-targeting therapies on the horizon

Classical | Lectin | Alternative
---|---|---

DISEASE

IC-MPGN
C3G
IgAN
IMN

COMPLEMENT-TARGETING THERAPIES

Soluble CR1
Anti-Factor B
Anti-Factor D
Anti-Properdin
Anti-C3 (Compstatin)
Aurin tricarboxylic acid

AAV
GPA

Anti-C5
C5 siRNA
C5aR antagonist (CCX168)

aHUS

Anti-C5a
Anti-C5
Aurin tricarboxylic acid

Courtesy Prof Christoph Licht
Genetic, serological, histological fingerprinting for targeted therapy

Terminal pathway activation due to dysregulation of all pathways: block the C5 convertase
- Anti-C5 (Eculizumab)
- C5 siRNA
- C5aR antagonist (CCX168-Avacopan)

Alternative pathway activation in the fluid phase: block the C3 convertase
- Anti-Factor B
- Anti-Factor D (Lampalizumab, ACH-4471)
- Anti-C3 (Compstatin)
- Properdin inhibitor
- Recombinant FH

Alternative pathway activation in the solid phase: block the C3 convertase at sites of local (endothelial or glomerular) activation
- TT30
THANK YOU

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• Dr Marina Noris
• Dr Elena Bresin
• Dr Veronique Fremeaux-Bacchi

• Prof Francesco Emma

The patients and their families
NEXT WEBINAR:

Olivia Boyer

“Genetic forms of podocytopathies in adults”

MARCH 13, 4-5 pm