C3 Glomerululopathy: The Past, Present, and Future of Treatment Paradigms

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MPGN: The Past Disease Paradigm

- **MPGN Type I**
  - Classical pathway activation by immune complexes
    - Typically low C3 and C4, subendothelial deposits on EM

- **MPGN Type II**
  - Alternative pathway activation (i.e. C3NeF, Factor H deficiency)
    - Typically very low C3 but normal C4
    - Intramembranous, very dense ribbon-like deposits on EM

- **MPGN Type III (Strife, Anders variants)**
  - Alternative and terminal pathway activation (C3NeF)
    - Low C3 and normal C4, subendothelial & subepithelial deposits, basement membrane fragmentation on EM
MPGN: The Past Treatment Paradigm

- **Corticosteroids**
    - Prednisone 40mg/m² every other day, mean duration 41 months
    - Favorable response to long term course of steroids, but with significant steroid toxicity noted
    - Prednisone 2mg/kg every other day initially, slowly reduced over 6-8 years
    - Earlier treatment (<1 yr after diagnosis) = favorable outcome
    - MPGN Type I with greater response than MPGN Type III

- **Cyclophosphamide, calcineurin inhibitors, MMF, rituximab also used in small studies**
C3G and IC-MPGN: The New Classification System

- Depends on magnitude of C3 staining on kidney biopsy (Fakhouri et al, *Nat Rev Nephrol* 2010)
  - Categorized by mechanism of disease (presence or scarcity/absence of immunoglobulin staining on IF)
  - C3G: Isolated or Predominant C3 staining
  - IC-MPGN: C3 staining \(\leq\) IgG/IgA/IgM
- Replaced classification of MPGN types I, II, III
C3 Glomerulopathy

• Consists of two diseases: Dense Deposit Disease (DDD) and C3 Glomerulonephritis (C3GN)
  – Due to defective regulation of alternative complement pathway
    • Typically low C3, normal C4
    • Autoantibody mediated (C3 Nephritic Factor [C3NeF], C4NeF, C5NeF, Factor H Autoantibody, Factor B Autoantibody) in 80% of DDD, ~50-60% of C3GN
    • Genetic abnormality (CFH mutations and polymorphisms, C3 and CFB mutations) in ~10-15% of DDD and C3GN
  – Clinical presentation for both entities variable
    • Asymptomatic microscopic hematuria/proteinuria, acute glomerulonephritis, nephrotic syndrome, RPGN
C3 Glomerulopathy

- Treatment Paradigms: The Present
  - Immunosuppression
    - Based on treatments found to be effective in some patients with the previous entity, MPGN
  - Complement-Targeted Therapy
    - Based on newer understanding of the pathomechanisms of C3 Glomerulopathy

Children's Hospital Colorado

Affiliated with
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Immunosuppression in C3G

• Retrospective Cohort Study by Rabasco et al (Kidney Int, 2015)
• 60 Patients with C3GN
  – 20 patients with no IST (supportive care only)
  – 22 patients treated with MMF + corticosteroids
  – 18 patients treated with other IST regimens
  – 90% of patients also treated with ACEi/ARB
  – Median followup of 47 months (range 16-93 months)
Immunosuppression in C3G

• IST dosing
  – Corticosteroids started 1mg/kg/d initially, “slowly tapering” to maintenance doses of 2.5-5mg/day or completely withdrawing
  – In MMF-IST group, MMF median initial dose 1g/day (range 0.75-2g/day) and median duration of 18 months (range 10-49 months)
  – In Other IST group, corticosteroids alone or corticosteroids + cyclophosphamide
Immunosuppression in C3G

Results

- ESRD in 10/60 patients (17% of cohort)
  - 7/20 (35%) of Non-IST patients \( p = 0.012 \)
  - 3/40 (7%) in IST patients

- Doubling Scr in 14/60 patients (23% of cohort)
  - 7/20 (35%) of Non-IST patients \( p = 0.195 \) (NS)
  - 7/40 (17%) in IST patients
Immunosuppression in C3G

Results

Remission

- Complete remission = eGFR > 60 or within 15% of baseline, proteinuria <0.5g/24 hr
- Partial remission = Proteinuria reduction by >50% and <3.5g/24 hr, stabilization or improvement in renal function

- 5/20 (25%) of Non-IST patients - CR 2 pts, PR 3 pts
- 28/40 (70%) in IST patients – CR 11 pts, PR 17 pts
  - 19/22 (86%) of MMF + corticosteroids IST
  - 9/18 (50%) of Other IST

- Greatest benefit appeared to be in C3NeF (+) pts
  - ? Autoantibody reduction by IST

p = 0.002
p = 0.018
Immunosuppression in C3G: Rebuttal

• Retrospective Cohort Study by Caliskan et al (Am J Nephrol 2017)
  – 66 Patients with C3G (7 pts DDD, 59 pts C3GN) treated with pre-determined protocol
    • 16 patients with supportive care (ACEi/ARB only)
    • 27 patients treated with MMF + low dose prednisolone (0.15mg/kg/d initially, tapered to 4mg/d by 4-8 weeks)
    • 23 patients treated with other IS regimens
      – Prednisolone alone, cyclophosphamide + prednisolone
  • All patients had supportive care with ACEi/ARB
    – Median followup of 44 months
Immunosuppression in C3G: Rebuttal

• Results
  – eGFR decline >50% in 17/66 patients (26% of cohort)
    • 5/16 (31%) of Non-IS patients
    • 4/23 (17.4%) in Other IS patients  \( p = NS \)
    • 8/27 (29.6%) in MMF-based IS patients
  – ESRD in 15/66 patients (23% of cohort)
    • 4/16 (25%) of Non-IS patients
    • 4/23 (17.4%) in Other IS patients  \( p = NS \)
    • 7/27 (25.9%) in MMF-based IS patients
Immunosuppression in C3G: Rebuttal

• **Results**
  
  – **Remission**
    
    • Complete remission = eGFR > 60 or within 15% of baseline, proteinuria <0.5g/24 hr
    
    • Partial remission = Proteinuria reduction by >50% and <3.5g/24 hr, stabilization or improvement in renal function

    • 9/16 (56%) of Non-IS patients - CR 3 pts, PR 6 pts
    
    • 16/27 (59%) in MMF-based IS patients – CR 11 pts, PR 5 pts
    
    • 16/23 (70%) in Other IS patients – CR 7 pts, PR 9 pts

    \[ p = \text{NS} \]
Immunosuppression in C3G: Rebuttal of Rebuttal?

- Retrospective Chart Review by Avasare et al (CJASN, 2018)
- 30 Patients with C3G (1 DDD, 29 C3GN)
  - Treated with MMF 1000mg twice daily x 3 months minimum
  - 28 patients (93%) also received corticosteroids at physician’s discretion - dose not specified
  - 25 patients (83%) also treated with stable dose of ACEi/ARB for antiproteinuric therapy throughout study
  - Median followup of 32 months (range 21-68 months)
Immunosuppression in C3G: Rebuttal of Rebuttal?

- **Results**
  
  - Complete remission = eGFR improved or within 15% of baseline with decline of proteinuria < 0.5g/g Cr
  
  - Partial remission = eGFR improved or within 15% of baseline with proteinuria reduction by ≥50% and between 0.5g and 3.5g/g Cr
  
  - 20 responders achieved complete (n = 10) or partial (n = 10) remission
    
    - Median time to remission from MMF initiation 291 days
  
  - 10 non-responders
    
    - 3/10 non responders progressed to ESRD
Immunosuppression in C3G: Rebuttal of Rebuttal?

Followup

- 8 of 20 responders to MMF tapered off immunosuppression
  - 4 of these 8 patients relapsed within 6 month to 2 years after discontinuation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders, n=20</th>
<th>Nonresponders, n=10</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>10 (50%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>10 (50%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Time to remission, mo</td>
<td>10 (3-12)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Proteinuria, mg/g creatinine</td>
<td>729 (215–1619)</td>
<td>5950 (1766–9125)</td>
<td>&lt;0.01</td>
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<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.11 (0.70–1.31)</td>
<td>1.85 (1.02–3.56)</td>
<td>0.01</td>
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<tr>
<td>ESKD</td>
<td>0</td>
<td>3</td>
<td>0.03</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Relapse off medication</td>
<td>4/8 (50%)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
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Values are presented as number (percentage) or median (interquartile range). NA, not applicable.
Complement-Targeted Therapy in C3G

• Currently only one approved tool in the toolbox = Eculizumab

• Proven efficacy in other complement-mediated diseases
  – PNH (FDA approved in 2009)
  – aHUS (FDA approved in 2011)

• Since approval, eculizumab used off-label to treat other diseases in which complement is a direct or indirect mediator
Pharmacology of Eculizumab

- Humanized monoclonal antibody against complement C5
  - High affinity binding to C5, prevents cleavage to C5a and C5b
    - Prevents activation of terminal complement pathway
  - Proximal pathways intact
    - Limitation in the treatment of alternative pathway dysregulation
Evidence for Complement-Targeted Therapy in C3 Glomerulopathy

- Animal model supports terminal pathway role in C3G
  - Cfh⁻/⁻ C5⁻/⁻ mice with reduced glomerular inflammation of spontaneous MPGN compared to Cfh⁻/⁻ mice
    - Similar GBM thickening, deposit formation
    - Improved SCr and mortality in Cfh⁻/⁻ C5⁻/⁻ at 12 months of age
    - No significant improvement in albuminuria

<table>
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<tr>
<th>Mice</th>
<th>n</th>
<th>GBM double contours, %</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>Median no. of glomerular neutrophils per gcs (range)</th>
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<tbody>
<tr>
<td>C5⁻/⁻</td>
<td>29</td>
<td></td>
<td>0</td>
<td>25</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0.04 (0–0.24)</td>
</tr>
<tr>
<td>Cfh⁻/⁻</td>
<td>19</td>
<td></td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>9</td>
<td>0.42² (0.08–1.16)</td>
</tr>
<tr>
<td>Cfh⁻/⁻ C5⁻/⁻</td>
<td>32</td>
<td></td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>18</td>
<td>6</td>
<td>0.16 (0–0.4)</td>
</tr>
</tbody>
</table>
Evidence for Complement-Targeted Therapy in C3 Glomerulopathy

- Clinical evidence
  - Some forms of C3NeF known to activate terminal pathway (C5 to C9)
  - Complement profiles of C3GN and DDD indicate alternative and terminal pathway activation
    - Terminal pathway activation appears to be more prominent in C3GN than in DDD

Zhang et al, CJASN 2014
Complement-Targeted Therapy in C3G

- Prospective, Open-label Proof of Concept Study by Bomback et al (CJASN 2012)
  - Standardized treatment regimen based on aHUS dosing of 900mg q.wk x 4, then 1200mg q.o. wk x 12 months
  - Patients on IS were tapered off during 1st 6 months
  - Suppression of CH50 on eculizumab therapy (0-6 CAE, nl range 60-144 CAE)

  - CH50 low at baseline in 5 of 6 pts (0-49 CAE) - may not be a sufficiently suitable pharmacodynamic biomarker in this disease
Complement-Targeted Therapy in C3G

• Methods – Baseline Patient Characteristics
  – All 6 pts were white male adults (range 20-42 yrs)
  – 3/6 pts w/ recurrent disease in renal allograft
    • 1 DDD, 2 C3GN
  – 5/6 pts previously treated with immunosuppression
  – 6/6 pts had impaired renal function at baseline
    • Median SCr 1.75 mg/dl (range 1.2–2.0 mg/dl).
  – 4/6 pts had nephrotic range proteinuria and/or significant hypoalbuminemia at initiation of therapy
  – Low C3 in 6/6 pts (range 27-80mg/dl, nl 83-177 mg/dl)
Complement-Targeted Therapy in C3G

• Results
  – Response appeared to depend on extent of terminal pathway activation with elevation in sC5b-9

<table>
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<tr>
<th>ID</th>
<th>sMAC (C5b-9; nl&lt;0.30 mg/L)</th>
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<tbody>
<tr>
<td>DDD1</td>
<td>1.08</td>
</tr>
<tr>
<td>DDD2</td>
<td>0.21</td>
</tr>
<tr>
<td>DDD3</td>
<td>0.07</td>
</tr>
<tr>
<td>C3GN1</td>
<td>0.71</td>
</tr>
<tr>
<td>C3GN2</td>
<td>0.32</td>
</tr>
<tr>
<td>C3GN3</td>
<td></td>
</tr>
</tbody>
</table>

↓Cr, no ∆ in mild proteinuria
↑Cr, ↑ proteinuria
↑Cr, ↓ proteinuria
↑Cr, no ∆ proteinuria
No ∆ Cr, no ∆ proteinuria
↓Cr (no proteinuria)

Complement-Targeted Therapy in C3G

- Other experience
    - 5 patients, all with DDD (age range 1.9-12.9 yrs)
    - C3 low in all patients, sC5b-9 elevated in 3 of 5 patients
    - Standard pediatric aHUS dosing regimen
    - Improvement in SCr and UPro/Cr in all 5 patients to varying degrees
      - Not correlated to sC5b-9 level
    - Leukocyturia resolved with eculizumab in all 5 patients
Complement-Targeted Therapy in C3G

- Other experience
    - 4 patients, all with improved UPro/Cr on eculizumab
    - All discontinued therapy, with relapse of disease
    - Resumption of eculizumab lead to improvement
Specifically targeting the alternative complement pathway may have greater efficacy in C3G

- C3 inhibitor (Amyndas, Apellis)
- Factor D inhibitor (Achillion)
- Factor D monoclonal Ab (Novartis)
- Factor B monoclonal Ab (Novelmed)
- sCR1 (Zhang et al, JASN 2013; Inflazyme)
Pharmacology of AP Inhibition

- **ACH-0144471**
  - Oral small molecule inhibitor of Factor D
  - Specific inhibitor of the alternative pathway, leaving classical pathway intact

- **APL-2**
  - PEGylated compstatin derivate (C3 inhibitor), administered subcutaneously
Factor D Inhibition in C3G

- Phase 2, Proof of Concept Study of Factor D Inhibitor ACH-0144471 in C3 Glomerulopathy (NCT03369236)
  - Sponsor = Achillion Pharmaceuticals
  - Design = Randomized, Double-Blinded, Placebo-controlled
  - Administration = Oral agent
  - 6 month Treatment Period
  - Recruiting patients ≥18 years of age with C3G with significant proteinuria (>1g/day), eGFR >30mL/min/1.73m²
C3 Inhibition in C3G

- Phase 2 Study of APL-2 in IgAN, SLE Nephritis, Primary Membranous Nephropathy, or C3G (NCT03369236)
  - Sponsor = Apellis Pharmaceuticals
  - Design = Open Label
  - Administration = Subcutaneous infusion once daily
  - 48 week Treatment Period
  - Recruiting patients ≥16, <70 years of age with C3G (as well as IgAN, SLE Nephritis, and primary MN) with significant proteinuria (>1.5g/day), eGFR >30mL/min/1.73m²
Summary

• Past treatment paradigms of MPGN were comprised of nontargeted immunosuppression

• Current paradigm differentiating pathobiology of C3G and immune complex MPGN suggests a disease-specific approach
  – Immunosuppression and eculizumab have both shown benefit in C3G
  – Neither, however, have proven to be uniformly efficacious, or with lasting benefit

• Alternative pathway-targeted therapies in clinical trials promise to directly target C3G pathomechanism