Emerging Biomarkers in Glomerular Diseases

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Biomarkers in Glomerular Disease

What is a good Biomarker - Useful for Diagnosis, Prognosis, Guide to Therapy?

Examples in Glomerular Disease:
- Anti-dsDNA Ab and complement in SLE-LN
- ANCA in small vessel vasculitis

What about idiopathic MN, IgAN, FSGS??

Membranous Nephropathy
Membranous Nephropathy: Overview

• Pathogenesis: subepithelial antigen-antibody immune-complex deposition
  - Diffuse granular IgG and complement deposition along GBM
  - Different isotypes depending on etiology (most common for iMN is IgG4)
  - Can also have mesangial immune complex deposition (more typical of secondary forms)

Secondary Membranous

• Causes
  - Autoimmunity: Lupus (Class V)
  - Alloimmunity: Allograft rejection, GVHD
  - Infections: Hepatitis B, some HCV, syphilis
  - Malignancy: esp. solid tumors
  - Medications: gold, mercury, penicillamine

• Diagnostic clues
  - Systemic disease
  - Demographics – less common in children and Blacks
  - Histology
    • Mesangial deposits
    • Tubuloreticular inclusions
    • Non-IgG4 immunoglobulins
    • TBM staining for IgG
    • Absence of PLA2R staining
**Phospholipase A2 Receptor**

- 185-kD glycoprotein present on **normal podocytes**
- Found in **immune deposits** of patients with idiopathic MN
- PLA2R and IgG4 **co-localize** on biopsy specimens from pts with idiopathic MN in a typical granular pattern
- ~70-80% of patients with idiopathic, **but not secondary, MN have antibodies against PLA2R**

Beck et al., NEJM, July 2, 2009  Rees & Kain, Nat.Reviews Neph 5, 617-618 2009

**PLA2R and IgG4 Co-Localize in Human**

Beck et al, NEJM 2009

**PLA2R in Idiopathic MN**
Genetics independently confirm association of PLA2R with iMN

Risk HLA-DQA1 and PLA2R1 Alleles in Idiopathic Membranous Nephropathy


-OR-

Could they have two separate diseases?

Sensitivity ~70%
Specificity ~88%


Anti-PLA2R is sensitive & specific for Idiopathic MN

Sensitivity ~70%
Specificity ~88%

Malignancy risk in membranous
aPLA-R positive vs. aPLA-R negative

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard ratio</th>
<th>99% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive aPLA-R</td>
<td>0.39</td>
<td>0.101–0.480</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.958</td>
<td>1.009–1.109</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>3.74</td>
<td>1.342–9.727</td>
<td>0.02</td>
</tr>
<tr>
<td>Proteinuria¹</td>
<td>1.101</td>
<td>1.034–1.176</td>
<td>0.003</td>
</tr>
<tr>
<td>Statin use</td>
<td>0.800</td>
<td>0.602–1.081</td>
<td>0.14</td>
</tr>
</tbody>
</table>

CI, confidence interval.
¹At the time of renal biopsy.

Malignancy occurrence:
aPLA-R negative: 10/27 (37%), sooner
aPLA-R positive: 6/64 (9%), later

Can Anti-PLA-R ab testing improve our ability to prognosticate in MN?

- Natural History is variable ("Rule of thirds")
  - 1/3 = Spontaneous remission
  - 1/3 = Persistent subnephrotic proteinuria
  - 1/3 = Persistent nephrotic syndrome, progressive CKD
    - Renal survival at 10 y: 65–85%
    - Renal survival at 15 y: 60%

Traditional risk factors for progression:
- Older Age
- Male Sex
- Reduced GFR
- Interstitial fibrosis on biopsy
- Heavy proteinuria, especially if persists

Risk factors for spont. remission:
- Baseline serum creatinine (mg/dl), HR 0.40 (0.19 to 0.85)
- Baseline proteinuria (g/24h), HR 0.85 (0.77 to 0.94)
- Proteinuria decrease >50% in the 1st year, HR 12.6 (5.2 to 30.5)
- ACEI/ARB use, HR 2.36 (1.09 to 5.12)

Patients with high-titer aPLA-R are unlikely to undergo spontaneous remission

<table>
<thead>
<tr>
<th>aPLA-R titer, by tertile</th>
<th>Low (n=26)</th>
<th>Middle (n=26)</th>
<th>High (n=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial remission</td>
<td>11 (42%)</td>
<td>8 (31%)</td>
<td>11 (41%)</td>
<td>NS</td>
</tr>
<tr>
<td>Complete remission</td>
<td>7 (27%)</td>
<td>9 (35%)</td>
<td>8 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>5 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Persistent proteinuria</td>
<td>7 (27%)</td>
<td>6 (23%)</td>
<td>3 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Spontaneous remission*</td>
<td>10 (38%)</td>
<td>8 (31%)</td>
<td>1 (4%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*No treatment with immunosuppressive agents
None of the patients with +PLA2R antibodies at the end of therapy had a persistent remission.

Progression of CKD in MN by tertile of aPLA2R Antibody level

Outcome:
- ≥25% rise in sCreat from baseline
- sCreat ≥1.3 mg/dl

Anti-PLA2R level correlates with disease activity in idiopathic MC

Hofstra J M et al. CJASN 2011;6:1286-1291
Disappearance of anti-PLA₂R precedes that of proteinuria


Time-course of anti-PLA₂R antibodies and proteinuria


Suggestions for practical use of anti-PLA₂R

1. If possible, every membranous nephropathy patient should have anti-PLA₂R assessed by biopsy and serum
2. In aPLA₂R-negative patients, look aggressively for secondary causes
3. For patients aPLA₂R positive on biopsy,
   - Absence of serum aPLA₂R may suggest impending remission
   - High-titer serum aPLA₂R may suggest low likelihood of remission
4. Assessing aPLA₂R at the end of immunosuppressive treatment may be useful in assessing likelihood of maintaining remission
5. Prospective studies using treatment algorithm based on anti-PLA₂R level are necessary for proof of concept
Anti-Phospholipase A2 Receptor Ab Titer Predicts Post-Ritux Outcome in iMN

- Retrospective review of 132 Pts with idiopathic MN treated with IV Rituximab.
- 84/132 had partial or complete remit.
- Of 81 with circulating anti-PLA2R Antibody, low Antibody titer and full Antibody depletion with Rituximab predicts remission.
- All 25 complete remitters had complete Antibody depletion.
- Re-emergence of Antibody predicted relapse.
- Assessing circulating anti-PLA2R auto-antibodies may help monitor disease activity and guide personalized rituximab therapy.

Piero Ruggenenti et al. JASN 26: 2545-2558, Oct 2015

Anti-PLA2R levels, but not CD20 counts, are associated with outcome after RTX

Proteinuria

Circulating CD20 cell counts

serum anti-PLA2R autoantibody levels

© 2015 by American Society of Nephrology

Anti-PLA2R levels, but not CD20 counts, are associated with outcome after RTX

IgA Nephropathy

IgA Nephropathy
The level of galactose-deficient IgA1 in the sera of patients with IgA nephropathy is associated with disease progression.

Na Zhao, Ping Hou, Jicheng Lv, Zina Moldoveanu, Yifu Li, Krzysztof Kiryluk, Ali G Gharavi, Jan Novak and Hong Zhang
Kaplan–Meier survival curves without dialysis/death event, with time zero set at diagnosis and elevated serum levels of autoantibodies (IgG >1.33 OD and/or IgA >1.79 U/ml) at diagnosis in IgAN patients.

Berthoux F et al. JASN 2012;23:1579-1587

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GWAS for IgA Nephropathy
20,612 individuals

Multiple signals
- HLA-DQ/DR
- HLA-DP
- HLA-DQ/DP

Observed (-LogP)
19 independent risk alleles
- (10 distinct genomic regions)
- Disease variance explained:
  - 8% in Asians, 6% in Europeans

Kiryluk et al. Nat Gen (2014)

GWAS and Pathogenesis Model

Dysregulated response to mucosal antigens
- TNFSF13, LIF/OSM
- CARD9, VAV3, DEFA

Defect in adaptive immunity
- HLA alleles
- MHC

Adaptive Immunity
- Defect in adaptive immunity
- MHC alleles

Complement System
- Inflammation and injury
- Complement activation
- Defects in CFHR1 and CFHR3
- Complement-activated C3 and C5a

Magistroni et al. Kid Int 2015 (in press)
Circulating Urokinase Receptor as a Cause of FSGS
Wei C, El hindi S, Li J, ... Reiser J.
Nature Medicine 17:952, 2011

Circulating suPAR Levels in Patients with CKD –
Are Serum suPAR Levels by Current ELISA reliable diagnostic biomarkers for FSGS

1) Elevated suPAR levels occur in ½ children and adults with Neph Synd and other renal disease
2) SuPAR levels correlate inversely with GFR
3) suPAR levels correlate with CRP (inflammation)
4) Results were evaluated by same ELISAs as original results
5) Elevated levels do not distinguish primary from secondary FSGS or other glomerular diseases


B7

B7 is a membrane protein found on activated antigen presenting cells.

When paired with CD28 or CD152 (CTLA-4) it produces co-stimulatory or co-inhibitory signals between the APC and the Tcells.

2 major B7 proteins B7-1 (CD80) and B7-2 (CD86).
Induction of B7-1 in podocytes is associated with Nephrotic Syndrome

Reiser J, von Gersdorff G, Loos M...Mundel P.
JCI 113:1390-1397, 2004

Role of B7-1 in podocytes as an inducible modifier of glomerular permselectivity.
B7-1 staining is NOT found in normal human podocytes.
B7-1 in podocytes was induced in genetic, drug-induced, immune mediated and bacterial toxin induced experimental kidney disease.
In human lupus nephritis podocyte expression of B7-1 correlated with the severity of the LN.
Mice lacking B7-1 protected form forms of induced nephrotic syndrome.

B7-1 Expression in murine and human podocytes correlates with proteinuria
A) Minimal in normal mouse – increased in NZB/W and at podocytes.
B) Localizes to glomeruli
D-E) Increase with proteinuria in human LN
E) Merge with synaptopodin.

Induction of B71 in podocytes of nephrin -/- mice vs WT
Since B7-1 is induced in podocytes in animal models of proteinuria, and B7-1 immunostaining found in 13/21 human biopsies with proteinuric kidney disease including FSGS — concluded B7-1 induced.

All transplant recurrent FSGS they found were + for B7-1 podocyte staining. Used abatacept to treat these patients.

Abatacept — a fusion protein of the Fc region of IgG1 fused to the extracellular domain of CTLA-4. Binds to CD80 (B7-1) and CD86 (B7-2) and prevents second signal of T cell activation.
**Abatacept in B7-1 Positive Proteinuric Kidney Disease**

- Abatacept (CTLA4-Ig), the co-stimulatory inhibitor targeting B7-1 (CD80), to treat FSGS.
- Report of 5 patients (4 rituximab resistant recurrent FSGS in the allograft - 2 lost prior kidney transplants due to recurrent FSGS and one glucocorticoid resistant FSGS in native kidney) all proteinuria, all +B7-1 immunostaining of podocytes.
- Elegant studies showing role of B7-1 in disrupting beta 1 integrin activation in podocytes.
- Abatacept induced partial or complete remission in all 5 patients “suggesting B7-1 may be a useful biomarker for treatment of some glomerulopathies.”


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**Abatacept Therapy for FSGS and GN???

Positive B7-1 staining of Bxs in other glomerular diseases. 3/5 MCD, 1/5 secondary FSGS, 3/3 Lupus GN, strongest staining in MN (PLA2R + or negative)

Urinary CD 80 (B7-1) is a marker of MCD not of FSGS.

Abatacept has failed a number of trials of Lupus Nephritis a disease where B7-1 (CD80) staining is consistently positive.

FSGS patients with failed results now being reported.

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**Negative Staining of FSGS Biopsies for B7-1**

Benigni A…Remuzzi G. NEJM 370:1259 March 27, 2014
Clinical Features and Response to B7-1 Blocker Therapy in FSGS


Figure 1. Immunohistochemical detection of B7-1 in a biopsy specimen from a patient with recurrent nephrotic syndrome after transplantation. (A) Interstitial activated B cells and monocytes show positive B7-1 staining. (B) Interstitial inflammatory cells show strong internal positive control staining for B7-1 while glomeruli are completely negative.

B7-1 Immunostaining in Proteinuric Kidney Disease


B7-1 Blockade Does Not Improve Post-Transplant Nephrotic Syndrome Caused by recurrent FSGS

Prospectively treated 9 patients with recurrent FSGS after transplant using either abatacept or belatacept (a B7-1 blocker with higher affinity) and did not produce proteinuria remission. Did NOT detect B7-1 expression by IF in podocytes of biopsy specimens from these or other kidney grafts or podocytes of native kidney biopsies specimens. In Conclusion, B7-1 blockade did not induce FSGS remission after transplantation in our study.

Delville M, Baye E, Durrbach A et al. JASN 2015-6
Abatacept does not improve albuminuria in patients with FSGS recurrence afterTx. Charts showing the post–Tx serum creatinine levels (black) and albuminuria-to-creatinine ratios (red) of (A) patient 1, (B) patient 2, (C) patient 3, (D) patient 4, and (E) patient 5.

Marianne Delville et al. JASN doi:10.1681/ASN.2015091002

Belatacept does not improve albuminuria in patients with FSGS recurrence after Tx. Charts showing the post–Tx serum creatinine levels (black) and albuminuria-to-creatinine ratios (red) of (A) patient 6, (B) patient 7, (C) patient 8, and (D) patient 9.

Marianne Delville et al. JASN doi:10.1681/ASN.2015091002

Dense Deposit Disease

Marianne Delville et al. JASN doi:10.1681/ASN.2015091002
C3 Glomerulonephritis

Immunofluorescence microscopy in Brad’s biopsy

- Focal endocapillary proliferative and exudative glomerulonephritis,
- with electron dense deposits in the intramembranous and mesangium
- consistent with dense deposit disease (MPGN type 2)

Complement Pathway

<table>
<thead>
<tr>
<th>Classical</th>
<th>Alternative</th>
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</thead>
<tbody>
<tr>
<td>C1</td>
<td>C3</td>
</tr>
<tr>
<td>C3</td>
<td>C3 convertase</td>
</tr>
<tr>
<td>C3a</td>
<td></td>
</tr>
<tr>
<td>C5</td>
<td>C5 convertase</td>
</tr>
<tr>
<td>C5a</td>
<td></td>
</tr>
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</table>

TRIGGERED BY ANTIGEN-ANTIBODY INTERACTION:
- Infection
- Cancer
- Auto-immune disease
- Allergic reaction
**Complement Pathway**

**Classical**
- C1
- C3
- C3b
- C5

**Alternative**
- C3 convertase
- C3 convertase
- C3a
- C5 convertase
- C5a

**Always On At Low Rate**

**Membrane Attack Complex**

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**Pathogenesis of the C3 glomerulopathies and reclassification of MPGN.**

Bomback AS, Appel GB.


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**Error: Image not loaded**
Patient Brad: Management

- Given minimal proteinuria and no specific therapies for C3 glomerulopathies in 2008, he was treated conservatively with losartan 25 mg daily

<table>
<thead>
<tr>
<th>Year</th>
<th>Creatinine</th>
<th>Proteinuria</th>
<th>C3</th>
<th>C4</th>
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<tbody>
<tr>
<td>2008</td>
<td>1.8</td>
<td>230</td>
<td>↓</td>
<td>nl</td>
</tr>
<tr>
<td>2009</td>
<td>1.9</td>
<td>500</td>
<td>↓</td>
<td>nl</td>
</tr>
<tr>
<td>2010</td>
<td>2.2</td>
<td>1000</td>
<td>↓</td>
<td>nl</td>
</tr>
</tbody>
</table>

2008 Biopsy:
- 0% glomerular scarring
- 0% interstitial scarring

2010 Biopsy
- 22% glomerular scarring
- 15% interstitial scarring
CUMC Eculizumab Pilot Study

<table>
<thead>
<tr>
<th>ID</th>
<th>Native/Transplant</th>
<th>Age</th>
<th>Race</th>
<th>Sex</th>
<th>Months from diagnosis</th>
<th>Previous Immunosuppression</th>
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</thead>
<tbody>
<tr>
<td>DDD1</td>
<td>Native</td>
<td>22</td>
<td>W</td>
<td>M</td>
<td>25</td>
<td>None</td>
</tr>
<tr>
<td>DDD2</td>
<td>Native</td>
<td>32</td>
<td>W</td>
<td>M</td>
<td>332</td>
<td>Steroids</td>
</tr>
<tr>
<td>DDD3</td>
<td>Transplant</td>
<td>42</td>
<td>W</td>
<td>M</td>
<td>150 (native) 0.5 (graft)</td>
<td>Steroids (native); tacrolimus and mycophenolate (graft)</td>
</tr>
<tr>
<td>C3GN1</td>
<td>Native</td>
<td>25</td>
<td>W</td>
<td>M</td>
<td>162</td>
<td>Steroids and mycophenolate</td>
</tr>
<tr>
<td>C3GN2</td>
<td>Transplant</td>
<td>22</td>
<td>W</td>
<td>M</td>
<td>138 (native) 8 (graft)</td>
<td>Steroids (native); steroids, tacrolimus, mycophenolate (graft)</td>
</tr>
<tr>
<td>C3GN3</td>
<td>Transplant</td>
<td>20</td>
<td>W</td>
<td>M</td>
<td>114 (native) 2 (graft)</td>
<td>Tacrolimus, mycophenolate, rituximab (native); steroids, tacrolimus, mycophenolate (graft)</td>
</tr>
</tbody>
</table>

Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis.

CUMC Eculizumab Pilot Study

<table>
<thead>
<tr>
<th>ID</th>
<th>CFH Mutation</th>
<th>CFI Mutation</th>
<th>MCP Mutation</th>
<th>C3 Nephritis Factor</th>
<th>Factor H Autoantibodies</th>
<th>Membrane Attack Complex</th>
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</thead>
<tbody>
<tr>
<td>DDD1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Negative</td>
<td>Negative</td>
<td>Elevated</td>
</tr>
<tr>
<td>DDD2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Positive</td>
<td>Negative</td>
<td>Normal</td>
</tr>
<tr>
<td>DDD3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Negative</td>
<td>Negative</td>
<td>-</td>
</tr>
<tr>
<td>C3GN1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Negative</td>
<td>Negative</td>
<td>Normal</td>
</tr>
<tr>
<td>C3GN2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Positive</td>
<td>Negative</td>
<td>Elevated</td>
</tr>
<tr>
<td>C3GN3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Positive</td>
<td>Negative</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

*Pre-treatment sample for sMAC testing not available in this subject; sMAC level at week 4 was normal

Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis.

CUMC Eculizumab Pilot Study

<table>
<thead>
<tr>
<th>ID</th>
<th>Treatment Time (weeks)</th>
<th>Creatinine</th>
<th>Proteinuria</th>
<th>Post-treatment Kidney Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDD1</td>
<td>52</td>
<td>↓</td>
<td>↓</td>
<td>Less inflammation</td>
</tr>
<tr>
<td>DDD2</td>
<td>40</td>
<td>Worsened</td>
<td>Worsened</td>
<td>Not performed</td>
</tr>
<tr>
<td>DDD3</td>
<td>52</td>
<td>Stable</td>
<td>↓</td>
<td>Less inflammation</td>
</tr>
<tr>
<td>C3GN1</td>
<td>52</td>
<td>Worsened</td>
<td>Stable</td>
<td>Increased scarring</td>
</tr>
<tr>
<td>C3GN2</td>
<td>52</td>
<td>Stable</td>
<td>↓</td>
<td>Less inflammation</td>
</tr>
<tr>
<td>C3GN3</td>
<td>52</td>
<td>↓</td>
<td>Stable</td>
<td>Less inflammation</td>
</tr>
</tbody>
</table>

Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis.
Resolution of endocapillary proliferation and exudative features

Partial resorption of electron dense deposits

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**Post-study follow-up for Brad (DDD1)**

<table>
<thead>
<tr>
<th></th>
<th>Creatinine (mg/dl)</th>
<th>Soluble MAC level (nl &lt;0.30 mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eculizumab</td>
<td>2.2</td>
<td>1.08</td>
</tr>
<tr>
<td>Study completion (1 year)</td>
<td>1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>3 months post-study</td>
<td>1.5</td>
<td>1.26</td>
</tr>
</tbody>
</table>

**RESTART ECULIZUMAB THERAPY**

<table>
<thead>
<tr>
<th></th>
<th>Creatinine (mg/dl)</th>
<th>Soluble MAC level (nl &lt;0.30 mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month into 2nd course of eculizumab</td>
<td>1.3</td>
<td>0.01</td>
</tr>
<tr>
<td>1 year into 2nd course of eculizumab</td>
<td>1.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*** JUST SIGNED A CONTRACT WITH NATIONAL HOCKEY LEAGUE FRANCHISE ***

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**MMF in C3 Gomelonephritis**

Rabasco C, Praga M GLOSEN - ASN Abstract 2014

- Multicenter, 60 Pts – 57% M mean age 37yo
- Presentation- 50% nephrotic, 33% nephritic, 17% asymptomatic urinary abnormalities
- 40/60 pts received immune modulatory meds (55% CS + MMF, 22% CS + other immune meds, 22% only CS) - Follow 48 months.
- Treated pts higher response (70% vs 30%), and Less ESRD (7% vs 35%)
MMF: A Drug for C3 Glomerulopathy?

**France**
- Chauvet et al.
- ASN Abstract 2012
- 9 patients treated with MMF
- 78% Renal survival at 12 months
- Median Follow-up time: 49 Months

**Spain**
- Praga et al.
- ASN Abstract 2014
- 22 patients treated with MMF
- 100% Renal survival at 50 months
- Median Follow-up time: 48 months

**Columbia University MMF Protocol (ASN 2015)**
- 98 patients with C3G
  - 76 with C3GN
  - 22 with DDD
- 25 patients received MMF
  - 24 with C3GN
  - 1 with DDD
- 24 Patients received MMF > 6 months
- 14 patients responded to MMF
  - 8 complete remission
  - 6 partial remission
- 1 patient did not tolerate MMF due to lymphopenia

Responders
- [C3](#): 82%
- [C4](#): 9%
- [C5b-9](#): 100%

Non-responders
- [C3](#): 57%
- [C4](#): 0%
- [C5b-9](#): 25%

\( p < 0.02 \)
Biomarkers for Glomerular Diseases

- What is a good Biomarker - Useful for Diagnosis, Prognosis, Guide to Therapy?
- Membranous Nephropathy – Yes – PLA2R - role is being defined.
- IgA – Galactose deficient IgA and Antibodies against it - needs more work and simple assays. Genetics may be answer.
- FSGS – Certainly not SuPAR.
  Role of B7-1 staining in glomerular disease is unclear. Regardless of B7-1 staining, the role of Abatacept needs more study.
C3GN – not C3 levels, ?Soluble MAC (C5b-9)???