MPGN

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- Membranoproliferative GN (MPGN), also termed mesangiocapillary GN, accounts for approximately 7%–10% of all cases of biopsy-confirmed GN .
- A light microscopic pattern of injury, MPGN occurs in both children and adults.
- The presentation is usually slowly progressive disease with hematuria and non-nephrotic proteinuria, but nephrotic syndrome.

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Editorial Reviews

NDT
Nephrology Dialysis Transplantation

The incidence of primary glomerulonephritis worldwide: a systematic review of the literature

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Abstract

Background. Little is known about the worldwide variation in incidence of primary glomerulonephritis (GN). The objective of this review was to critically appraise studies of incidence published in 1980–2010 so that an overall view of trends of these diseases can be found. This would little information on the epidemiology of these diseases is available from reviews. Insight into the baseline incidence of glomerulonephritis (GN) throughout the world can provide important information on trends of disease occurrence by sex, age and geographical location. New vaccines are being introduced and concerns have been raised about

Historical Classification

- The term MPGN refers to the features noted on (LM).

- characterized by
  - mesangial hypercellularity
  - endocapillary proliferation,
  - capillary wall remodeling
  - double contour formation
  - duplication of basement membranes .

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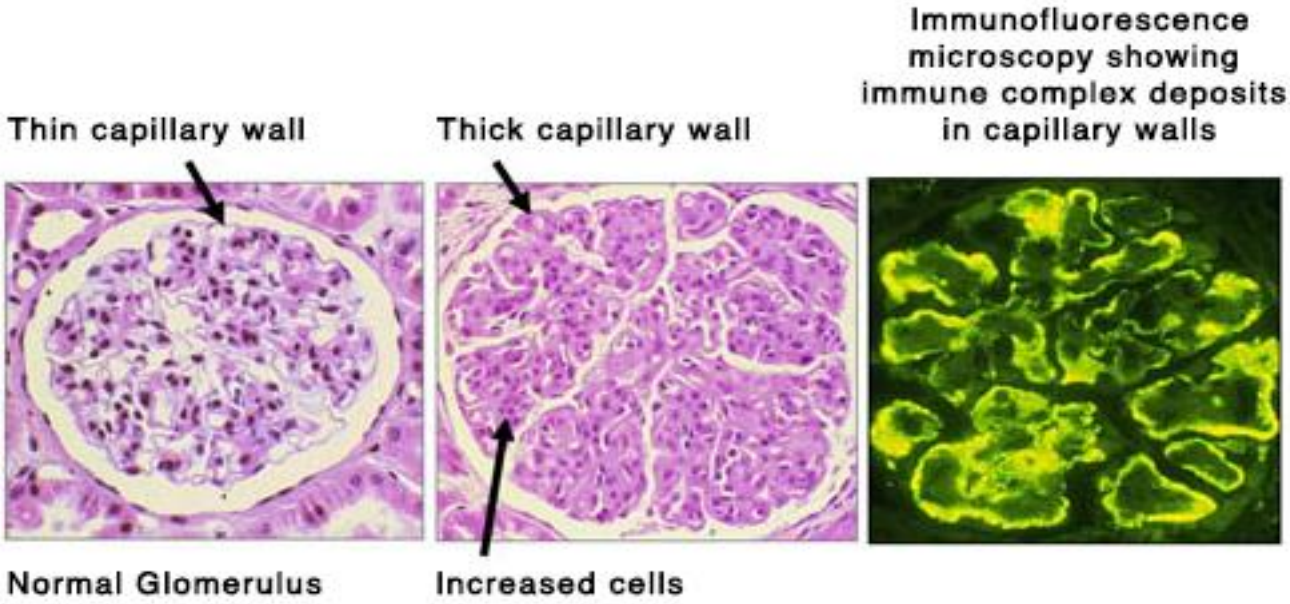
- MPGN I: subendothelial deposits
- MPGN III :subepithelial and subendothelial deposits .
- MPGN II :dense deposits in the glomerular basement membrane (dense deposit disease [DDD])

Membranoproliferative Glomerulonephritis Type I Glomerulus Viewed by Light Microscopy (left) and Immunofluorescence Microscopy (right)

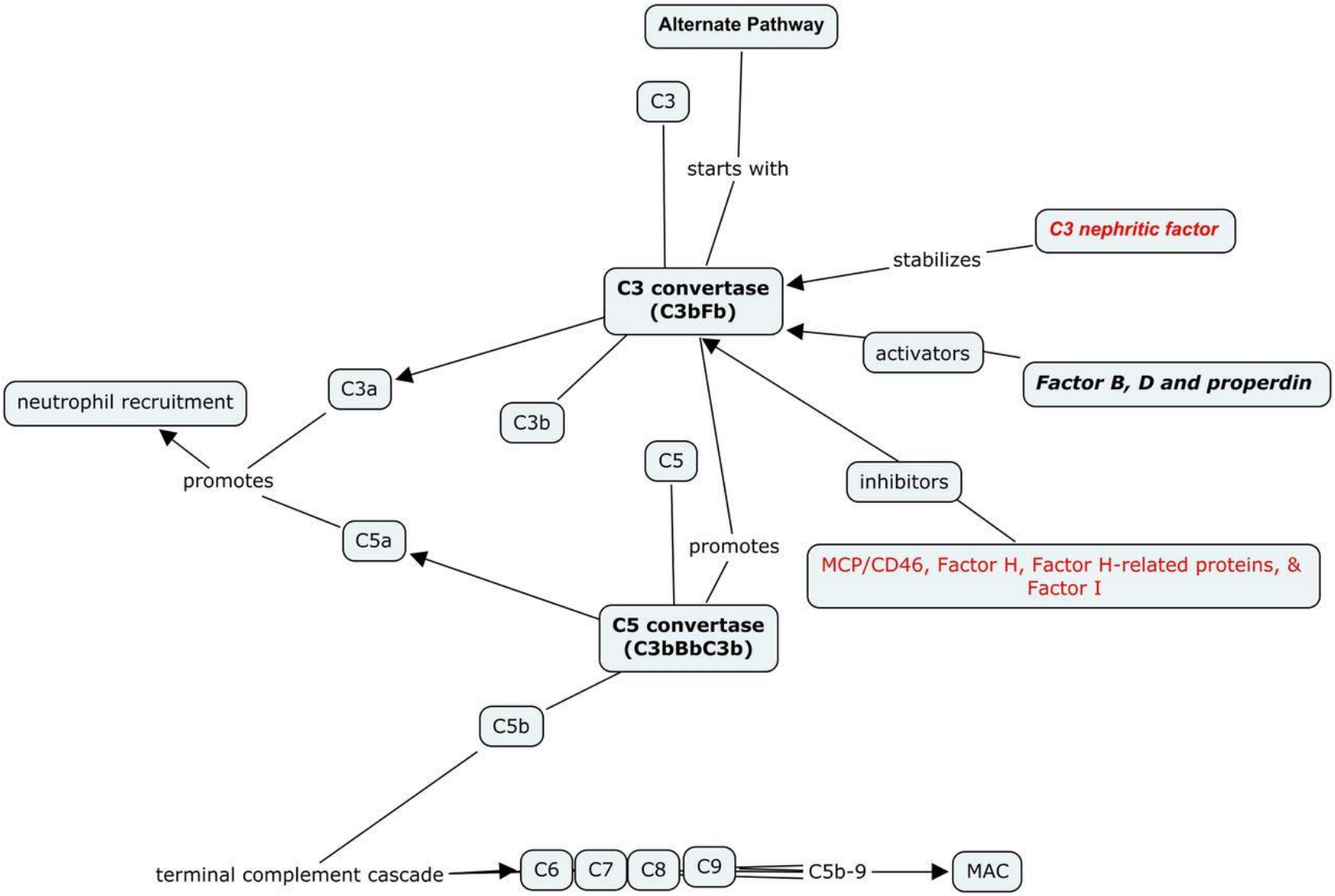


- The newer classification of MPGN is dependent on (IF) staining.
- Immune complex–mediated MPGN may occur when there are increased levels of circulating immune complexes.
- complement-mediated MPGN may occur because of dysregulation of the alternative pathway of complement.
- null complement and null immune complex chronic thrombotic microangiopathy may be the cause of the MPGN .

- The complement system is activated through three primary pathways—classic pathway, lectin pathway, and AP.
- The classic pathway and lectin pathway are triggered by Igs and bacterial carbohydrates.

- whereas the AP maintains low level of activity with mechanisms including activating and inhibitory proteins

Alternate pathway (AP) schematic.



Naveed Masani et al. CJASN 2014;9:600-608

CJASN

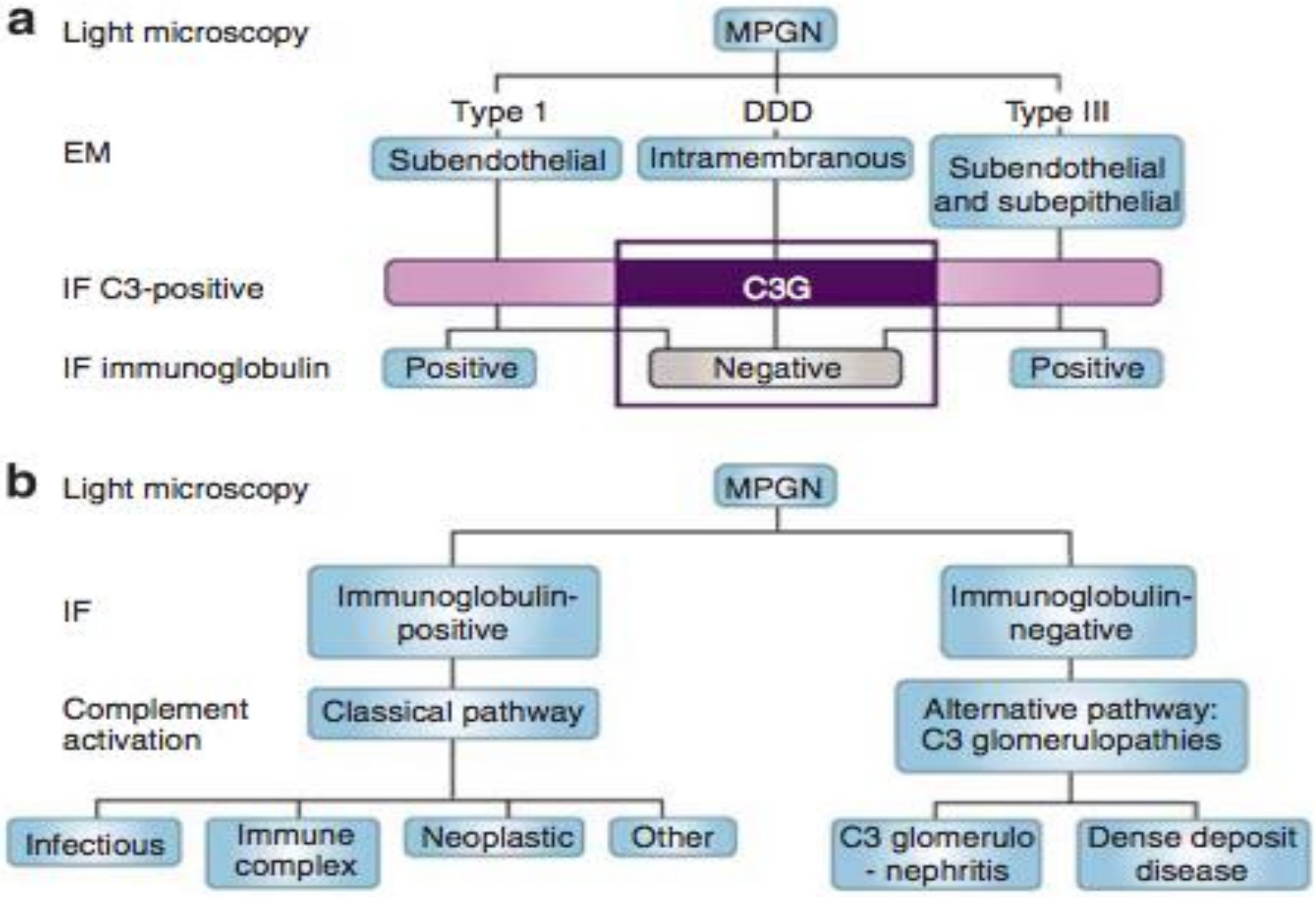


Figure 1 | The classification of membranoproliferative glomerulonephritis (MPGN) and C3 glomerulopathies (C3G) can overlap if based on electron microscopic findings.

- Activation of the AP begins with cleavage of C3 by C3 convertase, resulting in formation of C3a and C3b. Activators of the AP include factor B (FB) and factor D—both of which promote another generation of C3 convertase and lead to AP amplification .
- C3b interacts with FB. This C3bFB complex then interacts with factor D and results in a complex of C3 convertase with C3bFB, which then promotes formation of C5 convertase; C5 convertase cleaves C5 into C5a and C5b. C5a (along with C3a) acts as a chemoattractant, recruiting neutrophils and promoting an inflammatory cascade.
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- C5b leads to the final product of complement activation, C5b-C9 .The membrane attack complex leads to the formation of transmembrane pores, resulting in osmotically-driven water entry, which causes cell lysis .

- Inhibitors of the AP include factor H (FH) and its related proteins (FHRPs) factor I (FI), CD35, and membrane cofactor protein (MCP; also known as CD46). FH is the principal inhibitor, and mutations in FH or FHRP lead to significant AP dysregulation.

- C3 nephritic factor (C3Nef) is an autoantibody that stabilizes the activity of C3 convertase, making it resistant to the degradation effects of FH, thereby increasing the half-life of C3 convertase and promoting AP amplification. Approximately 80% of DDD patients are positive for C3Nef.
- However, C3Nef presence has also been shown in ~40% of C3GN patients, potentially nullifying its use as a specific marker for DDD

Dense deposit disease
(DDD)

C3 glomerulonephritis
(C3GN)

Older and newer classification of membranoproliferative GN

IF, immunofluorescence; MPGN, membranoproliferative GN.

	Based on Electron Microscopy (Older)	Based on Immunofluorescence (Newer)
Classification	MPGN 1: Subendothelial MPGN	Immune complex–mediated MPGN Igs and complements on IF (paraproteins, viruses, autoimmune)
	MPGN 2: Dense subendothelial deposits (dense deposit disease)	Complement-mediated MPGN C3 dominant IF (C3 glomerulopathy)
	MPGN 3: Subendothelial membranoproliferative with intramembranous and subepithelial deposits	MPGN not related to complement or immune complex
		Negative IF (thrombotic microangiopathy)

C3 Glomerulopathy: DDD and C3GN

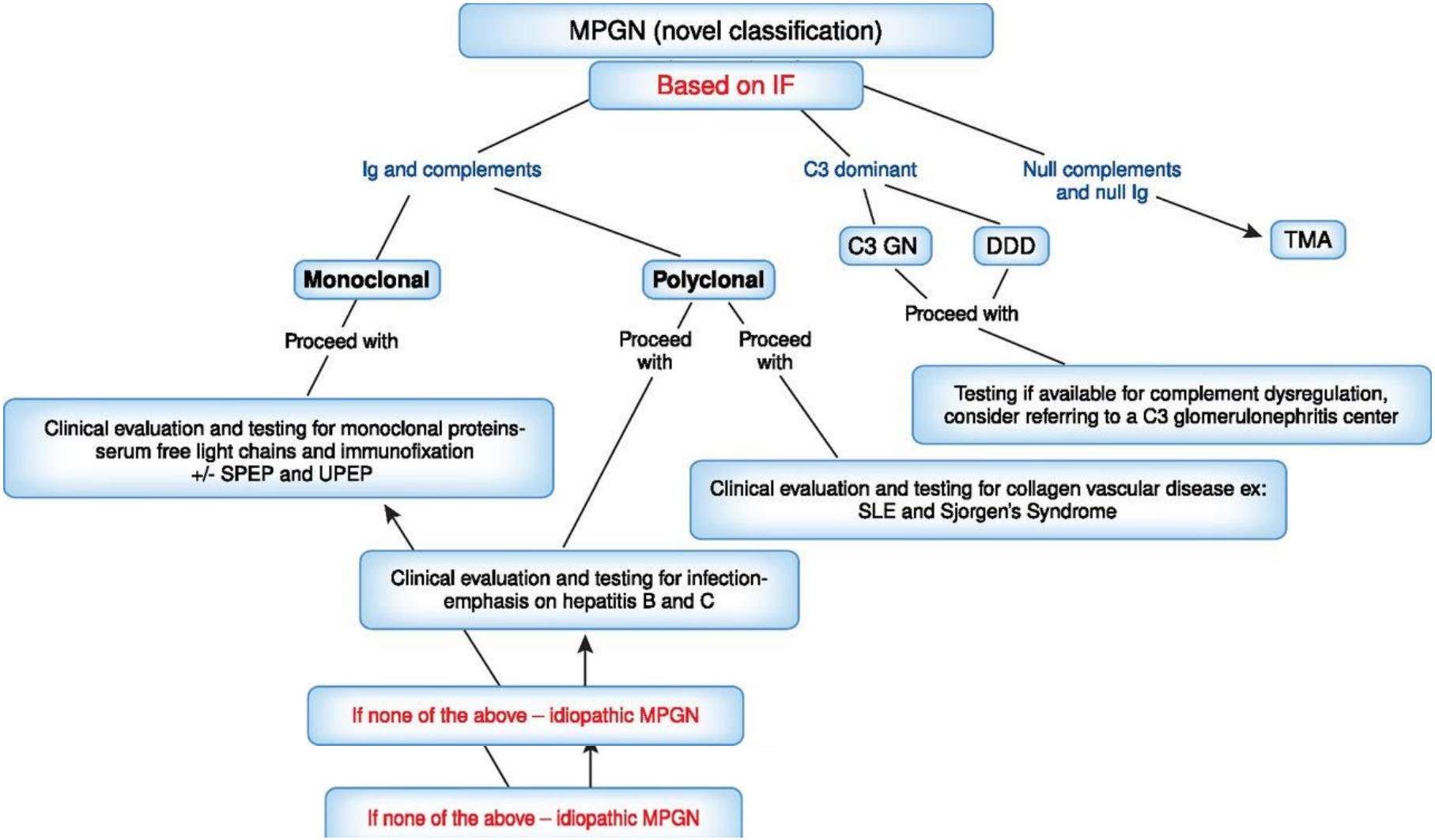
- The principal entities that represent C3 glomerulopathy are DDD, which is historically classified as MPGN II, and C3GN.
- EM aids in differentiating between these disorders.

mesangial deposits accompanied by highly dense intramembranous deposits suggest a diagnosis of DDD.

whereas the presence of deposits in mesangial, subendothelial, subepithelial, and/or intramembranous locations suggests C3GN.

the composition of the deposits in C3 glomerulopathy is typically devoid of Ig and consists mainly of complement proteins, particularly C3 and terminal complement components (C5b-C9).

Simplistic breakdown of the new MPGN classification using immunofluorescence as the basis and an approach to evaluation when the kidney biopsy indicated MPGN. DDD, dense deposit disease; IF, immunofluorescence; SPEP, serum protein electrophoresis; TMA, thro...



Naveed Masani et al. CJASN 2014;9:600-608

CJASN

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- DDD has also been associated with monoclonal gammopathy; some might have dominant C3 only on IF .

- In 2010, Martínez-Barricarte first described a C3 mutation in two patients with DDD from the same family. The mutation made C3 resistant to cleavage by C3 convertase, making the formation of C3b impossible. However, the mutated C3 did get cleaved by proteases and spontaneous hydrolysis, leading to formation of C3b and C3 convertase that were resistant to the breakdown efforts of FH.. It should be noted that the LM findings accompanying DDD are not limited to MPGN and can include mesangial proliferative as well as crescentric patterns of injury.

Known mutations/causes associated with C3GN

Autoantibodies to C3 convertase

Autoantibodies to factor H

Autoantibodies to factor B

Properdin deficiency

C3 nephretic factor

Complement factor H mutation screening identified the H402 allele and V62 allele

Heterozygous mutations in factor I gene

Heterozygous mutation in CD 46 gene (membrane cofactor protein)

Mutation in the gene for complement factor H-related protein 5

Thrombotic microangiopathies associated with MPGN pattern of injury

Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (resolving)

Antiphospholipid syndrome

Radiation nephropathy (bone marrow transplant-related nephropathy)

Sickle cell disease

Transplant glomerulopathy

- Sethi *et al.* described 12 cases of C3 glomerulopathy with varying LM

C3 glomerulopathy-associated CFHR1 mutation alters FHR oligomerization and complement regulation.

Tortajada A[1], Yébenes H, Abarrategui-Garrido C, Anter J, García-Fernández JM, Martínez-Barricarte R, Alba-Domínguez M, Malik TH, Bedoya R, Cabrera Pérez R, López Trascasa M, Pickering MC, Harris CL, Sánchez-Corral P, Llorca O, Rodríguez de Córdoba S.

Author information

Abstract

C3 glomerulopathies (C3G) are a group of severe renal diseases with distinct patterns of glomerular inflammation and C3 deposition caused by complement dysregulation. Here we report the identification of a familial C3G-associated genomic mutation in the gene complement factor H–related 1 (CFHR1), which encodes FHR1. The mutation resulted in the duplication of the N-terminal short consensus repeats (SCRs) that are conserved in FHR2 and FHR5. We determined that native FHR1, FHR2, and FHR5 circulate in plasma as homo- and hetero-oligomeric complexes, the formation of which is likely mediated by the conserved N-terminal domain. In mutant FHR1, duplication of the N-terminal domain resulted in the formation of unusually large multimeric FHR complexes that exhibited increased avidity for the FHR1 ligands C3b, iC3b, and C3dg and enhanced competition with complement factor H (FH) in surface plasmon resonance (SPR) studies and hemolytic assays. These data revealed that FHR1, FHR2, and FHR5 organize a combinatorial repertoire of oligomeric complexes and demonstrated that changes in FHR oligomerization influence the regulation of complement activation. In summary, our identification and characterization of a unique CFHR1 mutation provides insights into the biology of the FHRs and contributes to our understanding of the pathogenic mechanisms underlying C3G.

Dense deposit disease and glomerulonephritis with isolated C3 deposits are glomerulopathies characterized by deposits of C3 within or along the glomerular basement membrane. Previous studies found a link between dysregulation of the complement alternative pathway and the pathogenesis of these diseases. We analyzed the role of acquired and genetic complement abnormalities in a cohort of 134 patients, of whom 29 have dense deposit disease, 56 have glomerulonephritis with isolated C3 deposits, and 49 have primary membranoproliferative glomerulonephritis type I, with adult and pediatric onset. A total of 53 patients presented with a low C3 level, and 65 were positive for C3 nephritic factor that was significantly more frequently detected in patients with dense deposit disease than in other histological types. Mutations in CFH and CFI genes were identified in 24 patients associated with a C3 nephritic factor in half the cases. We found evidence for complement alternative pathway dysregulation in 26 patients with membranoproliferative glomerulonephritis type I. The complement factor H Y402H variant was significantly increased in dense deposit disease. We identified one at-risk membrane cofactor protein (MCP) haplotype for glomerulonephritis with isolated C3 deposits and membranoproliferative glomerulonephritis type I. Thus, our results suggest a critical role of fluid-phase alternative pathway dysregulation in the pathogenesis of C3 glomerulopathies as well as in immune complex-mediated glomerular diseases. The localization of the C3 deposits may be under the influence of MCP expression.

MPGN without Immune Complexes and Complement

- When pathology reveals no immune complex deposits and no specific IF staining but the light microscope reveals an MPGN pattern of injury, (TMA) is the most likely diagnosis.
- Injury to the endothelial cell can lead to a similar pattern without complement activation. Rennke discussed this possibility as early as 1995 among secondary causes of MPGN.
- With regards to transplant glomerulopathy, IF findings of null C3 and null Ig can aid in distinguishing from recurrent MPGN

Recurrence Post-Transplantation

- Post-transplant recurrence of MPGN has been reported with variable rates, in part depending on the underlying pathobiology. MPGN associated with monoclonal gammopathy seems to have an earlier recurrence with a more aggressive course. recurrence of MPGN in renal allografts is associated with the presence of crescents in the native kidneys as well as the allograft .

- One large study using the older classification of MPGN looked at recurrence rates in 88 patients with MPGN I .The incidence of allograft loss at 10 years because of recurrent MPGN I was 14.4% which was similar to the incidence of recurrent FSGS. In an analysis of nearly 190,000 renal transplant patients, the incidence of allograft loss at 10 years because of recurrent MPGN I was similarly 14.5%, which was higher than other glomerulonephritides combined .

- With regards to C3 glomerulopathy, DDD recurrence is the norm, with a 50% graft failure rate; data regarding C3GN recurrence is limited, but recurrence has been reported .Ten patients with CFHR5 nephropathy are reported with successful kidney transplantation .

N Engl J Med. 2002 Jul 11;347(2):103-9.

Risk of renal allograft loss from recurrent glomerulonephritis.

Briganti EM[1], Russ GR, McNeil JJ, Atkins RC, Chadban SJ.

Author information

Abstract

BACKGROUND:

Recurrent glomerulonephritis is a known cause of renal allograft loss; however, the incidence of this complication is poorly defined. We determined the incidence, timing, and relative importance of allograft loss due to the recurrence of glomerulonephritis.

METHODS:

A total of 1505 patients with biopsy-proved glomerulonephritis received a primary renal transplant in Australia from 1988 through 1997. Recurrence was confirmed by renal biopsy. The Kaplan-Meier method was used to estimate the 10-year incidence of allograft failure due to recurrent glomerulonephritis, and this incidence was compared with the incidence of acute rejection, chronic rejection, and death with a functioning allograft. Characteristics of the recipients and donors were examined as potential predictors of recurrence.

Recurrent membranoproliferative glomerulonephritis after kidney transplantation.

Lorenz EC[1], Sethi S, Leung N, Dispenzieri A, Fervenza FC, Cosio FG.

Author information

Abstract

On examination of the records of 1321 patients following kidney transplant over an 11-year period, we found that 29 patients had recurrent membranoproliferative glomerulonephritis (MPGN). We exclude from this analysis patients who had MPGN type II, those with clear evidence of secondary MPGN, and those lacking post-transplant biopsies. During an average of 53 months of follow-up, we found using protocol biopsies that 12 of these patients had recurrent MPGN diagnosed 1 week to 14 months post-transplant. In 4 of the 12 patients this presented clinically, whereas the remaining had subclinical disease The risk of recurrence was significantly increased in patients with low complement levels. Serum monoclonal proteins were found in a total of six patients; appeared to be associated with earlier, more aggressive disease; and were more common in recurrent than non-recurrent disease. The recurrence of MPGN was marginally higher in recipients of living-donor kidneys. Some patients developed characteristic lesions within 2 months post-transplant, whereas others presented with minimal, atypical histological changes that progressed to MPGN. Of 29 patients, 5 lost their allograft and 2 patients rem on chronic plasmapheresis. Our study shows the risk of MPGN recurrence and progression depends on identifiable pretransplant characteristics, has variable clinical impact, and can result in graft failure.

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20130531
DOI:
10.1038/ki.2010.1

8.1: Evaluation of MPGN

8.1.1: Evaluate patients with the histological (light microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20). (Not Graded)

Table 20 | Underlying conditions associated with a membranoproliferative pattern of GN

Chronic infections (especially hepatitis C)
Autoimmune diseases (especially LN)
Monoclonal gammopathies (especially light-chain deposition disease and monoclonal IgG disease)
Complement dysregulation (especially complement factor H deficiency)
Chronic and healed thrombotic microangiopathies

Evaluation of MPGN

- The evaluation of MPGN usually begins with recognition of the clinical syndrome of GN, which leads to a kidney biopsy. I
- When renal pathology IF shows Igs and C3 ($Ig^{+}C3^{+}$), then, MPGN is considered to be immune complex–mediated. a careful evaluation for infection I,
- serologies for evidence of infection with hepatitis B or C should be obtained.
- Another cause of immune complex–mediated MPGN is the presence of a monoclonal gammopathy. Of patients with MPGN without hepatitis B or C, 41% of patients have a monoclonal gammopathy of uncertain significance .Testing could include serum free monoclonal light chain analysis, immunofixation, and serum and urine protein electrophoresis. An additional cause of MPGN that is immune complex–mediated is SS..
- .

Evaluation of MPGN

- The greatest advances in MPGN have been in the area of complement-mediated disease. when renal pathology shows predominant staining for C3, a C3 glomerulopathy is present. Pathologic features help to further define the disease as DDD or C3GN.

Most patients will have persistently low levels of C3 and may be positive for C3 nephritic factor .testing to characterize the abnormalities leading to dysregulation of complement metabolism should be performed. Such testing is currently available only at select research laboratories. Tests of interest would include evaluation for antibodies associated with dysregulation of the alternative complement pathway, including C3Nef, anti–co-FB autoantibodies, anti-FH, and anti-FI. Genetic testing for key complement regulators, primarily co-FH, co-FI, MCP (CD46), and FH-related proteins, would be helpful if available

Treatment

it might be said that treatment for MPGN syndromes, in general, is not well established.

Treatment of the glomerulonephritis

- The treatment of secondary MPGN is directed at treatment of the underlying condition since the renal disease often resolves with treatment of causes such as infection, autoimmune disorders, and monoclonal gammopathy.
- Once treatable underlying causes of MPGN have been excluded, three conditions remain:
- ●Idiopathic immune complex-mediated MPGN
- ●C3 glomerulonephritis
- ●Dense deposit disease

- Poor prognostic signs at presentation include the nephrotic syndrome, an elevated serum creatinine, hypertension (or blood pressure well above the patient's previous baseline), and, on renal biopsy, crescents. Another important adverse prognostic sign on renal biopsy is tubulointerstitial disease (interstitial inflammation, fibrosis, and tubular atrophy

Immunosuppressive therapy

- Indications for immunosuppressive therapy include nephrotic range proteinuria, a reduced estimated glomerular filtration, and/or severe histologic changes on renal biopsy (eg, crescents) at baseline, and progressive disease over time with angiotensin inhibitors alone .

MPGN

- Prednisolon
- Cyclophosphamide
- Rituximab
- Mycophenolate mofetil
- Calcineurin inh.

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Review Article

Rituximab for Treatment of Membranoproliferative Glomerulonephritis and C3 Glomerulopathies

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Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

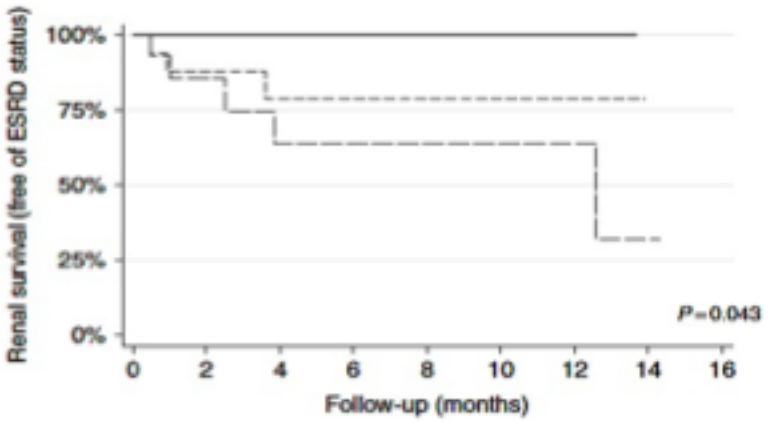
OPEN

Timothy H.J. Goodship[1], H. Terence Cook[2], Fadi Fakhouri[3], Fernando C. Fervenza[4], Véronique Frémeaux-Bacchi[5], David Kavanagh[1], Carla M. Nester[6,7], Marina Noris[8], Matthew C. Pickering[2], Santiago Rodríguez de Córdoba[9], Lubka T. Roumenina[10,11,12], Sanjeev Sethi[13] and Richard J.H. Smith[6,7]; for Conference Participants[14]

Kidney International (2017) 91, 539–551;

Table 5. Kidney International (2017) 91, 539–551;

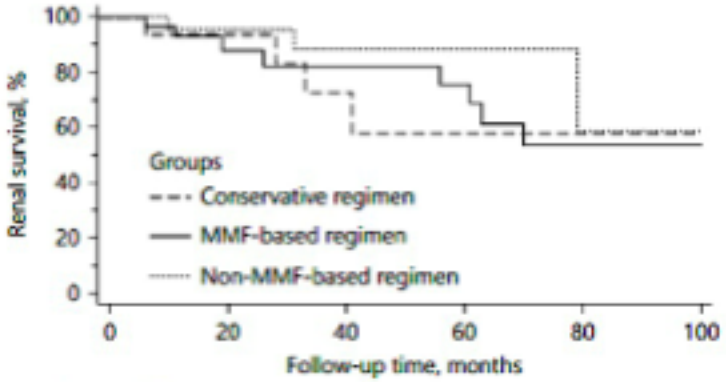
All Patients	• Optimal blood pressure control (Suggested: BP below the 90% in children and ≤ 120/80 in adults) ○ Priority agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers, • Optimal nutrition for both normal growth in children, healthy weight in adults • Lipid control
Moderate Disease	**Description** • Urine protein over 500mg/24 hours despite supportive therapy or • Moderate inflammation on renal biopsy or • Recent increase in serum creatinine suggesting risk for progressive disease **Recommendation** • Prednisone • Mycophenolate mofetil
Severe Disease	**Description** • Urine protein over 500mg/24 hours despite supportive therapy • Or Moderate inflammation on renal biopsy • Or recent increase in serum creatinine suggesting risk for progressive disease **Recommendation** • Methylprednisolone pulse dosing as well as other anti-cellular immune suppressants have had limited success in rapidly progressive disease • Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease.



MMF-IST ----- Other-IST
——— No IST

Patients at risk according to months of follow-up

Group of treatment	0	2	4	6	8	10	12	14	16
MMF-IST	22	15	10	5	4	4	2	1	1
Other-IST	18	13	10	6	4	2	2	1	1
No IST	20	14	11	7	6	6	5	4	3



Number at risk

Group: conservative regimen						
	16	12	5	4	3	2
Group: MMF-based regimen						
	27	18	15	11	4	4
Group: non-MMF-based regimen						
a	23	14	9	5	2	1

	No Immune Suppression	MMF	Other IST
Complete Remission	2/20 (40%)	6/22 (32%)	5/18 (56%
Partial Remission	3/20 (60%	13/22 (68%)	4/18 (44%)
ESRD	10/20 (35%	0/22 (0%)	3/18 (16%)

microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20). (*Not Graded*)

Table 20 | Underlying conditions associated with a membranoproliferative pattern of GN

Chronic infections (especially hepatitis C)
Autoimmune diseases (especially LN)
Monoclonal gammopathies (especially light-chain deposition disease and monoclonal IgG disease)
Complement dysregulation (especially complement factor H deficiency)
Chronic and healed thrombotic microangiopathies

GN, glomerulonephritis; LN, lupus nephritis.

1	☐	Active, not recruiting	Eculizumab in Primary **MPGN**	**Membranoproliferative Glomerulonephritis**	Drug: Eculizumab
2	☐	Recruiting	A Proof-of-Mechanism Study to Determine the Effect of ACH-0144471 on C3 Levels in Patients With C3G or IC-**MPGN**	C3 Glomerulonephritis Dense Deposit Disease **Membranoproliferative Glomerulonephritis**, Type II (and 2 more...)	Drug: ACH-0144471
3	☐	Not yet recruiting	Effect of Rituximab in Treatment of**Membranoproliferative Glomerulonephritis**	**Membranoproliferative Glomerulonephritis**	Drug: Rituximab Drug: Cyclosporin
4	☐	Recruiting	Daratumumab in Treatment of PGNMID and C3 GN	**Membranoproliferative Glomerulonephritis**	Drug: Daratumumab
5	☐	Completed	Pilot Study of Rituximab for**Membranoproliferative Glomerulonephritis**	Glomerulonephritis, Membranoproliferative	Drug: Rituximab
6	☐	Unknown †	Eculizumab Therapy for Dense Deposit Disease and C3 Nephropathy	Dense Deposit Disease **Membranoproliferative Glomerulonephritis**	Drug: Eculizumab
8	☐	Recruiting	Controlled Trial Evaluating Avacopan in C3 Glomerulopathy	C3 Glomerulopathy (C3G)	Drug: Avacopan Drug: Avacopan Matching Placebo

C3 glomerulopathy&DDD

- Disease due to an autoantibody: plasmaexchange,rituximab,eculizumab
- Genetic deficiency: FFP
- RPGN:pred+endoxane
- MGUS

THANK YOU