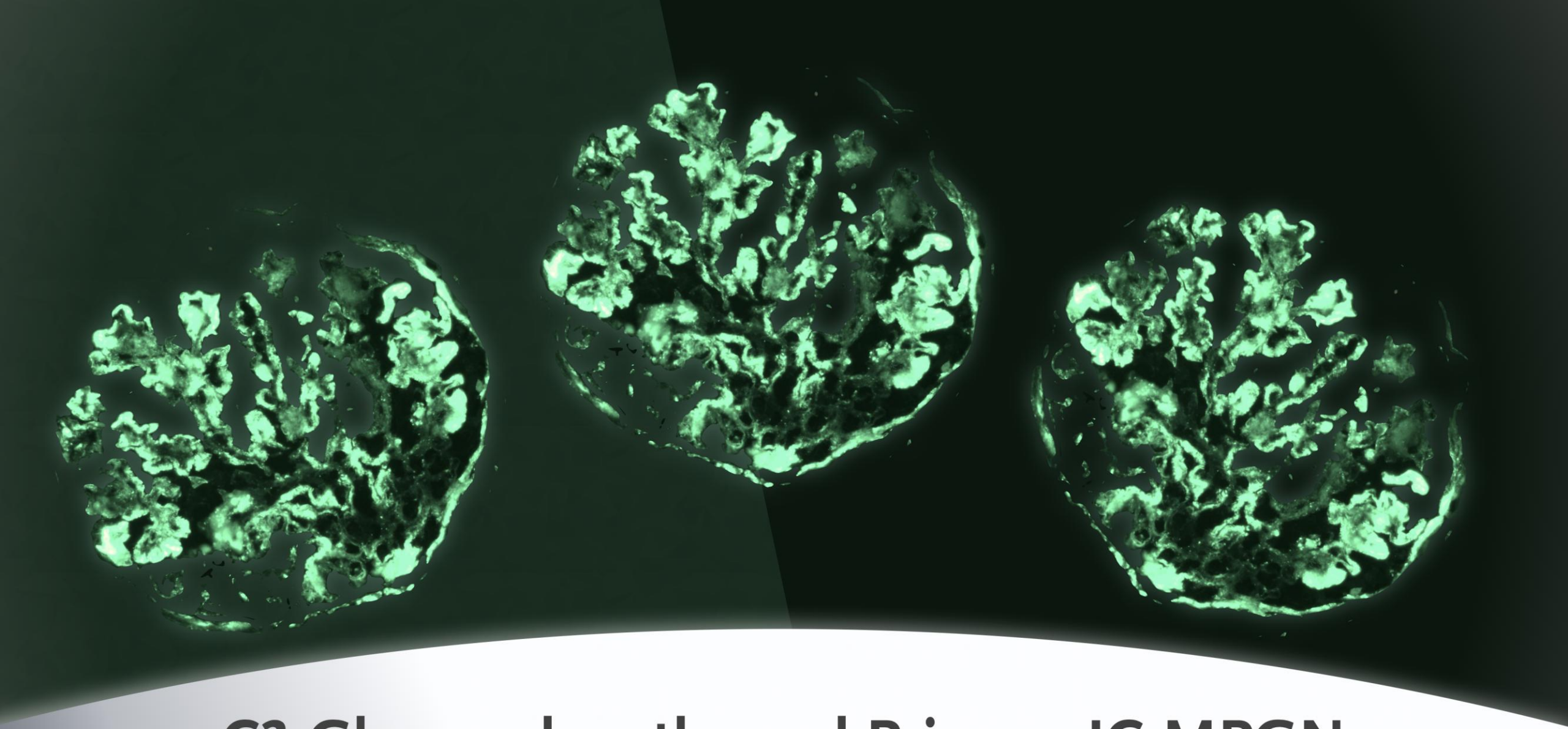
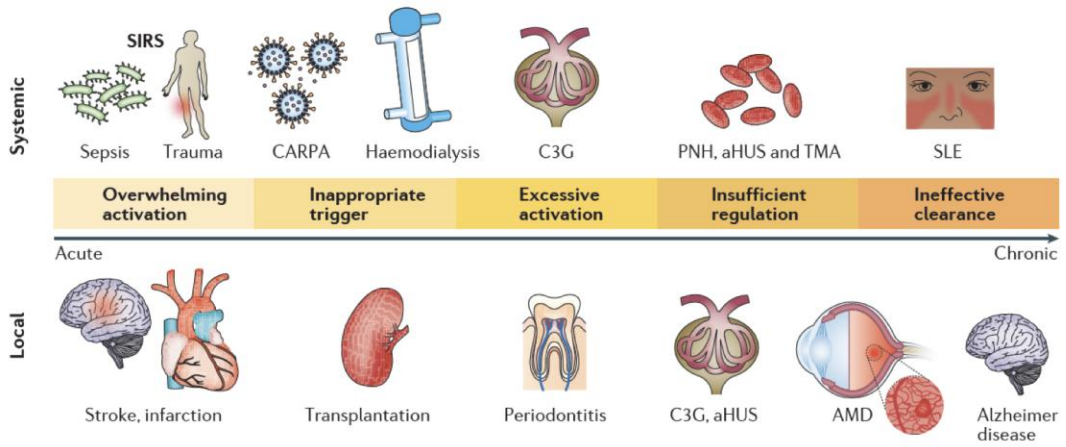


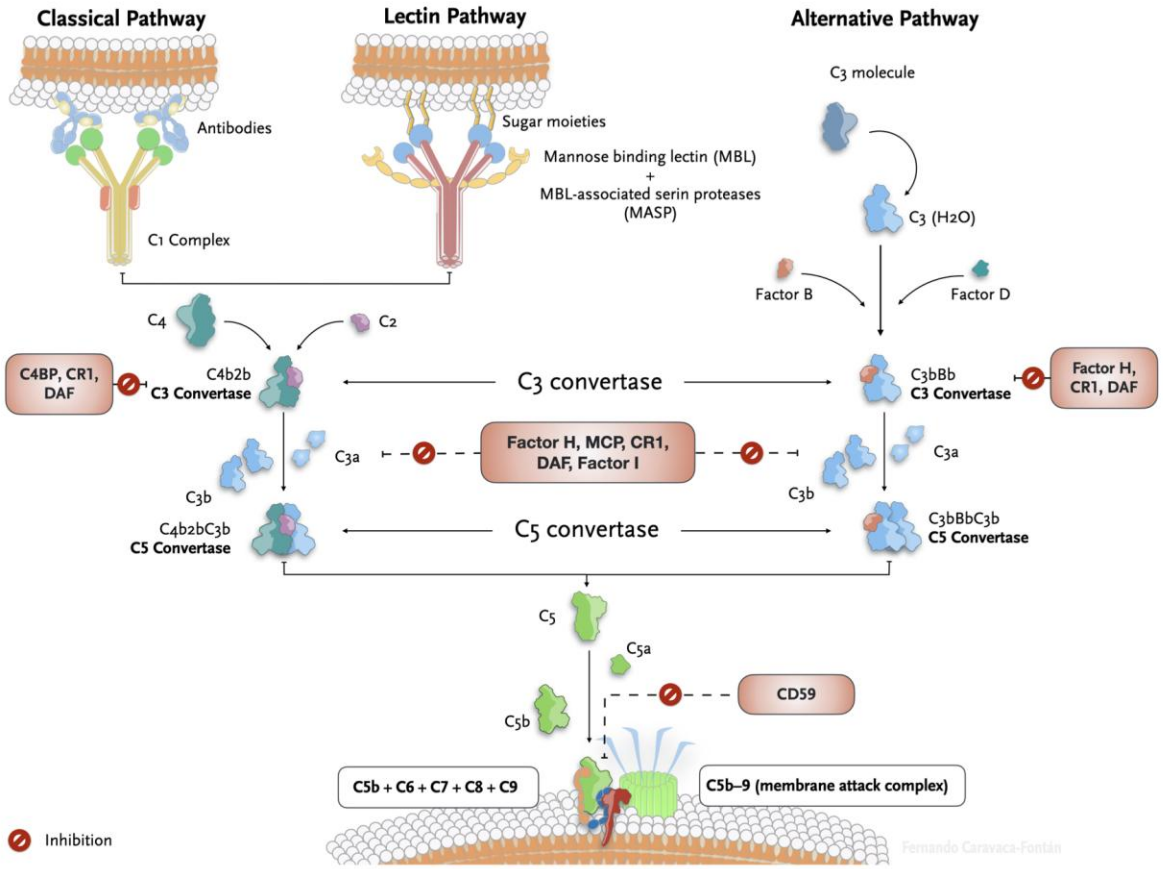
C3 Glomerulopathy and Primary IC-MPGN

Fernando Caravaca-Fontán
Research Institute Hospital 12 de Octubre, Madrid, Spain

C3 Glomerulopathy and Primary IC-MPGN

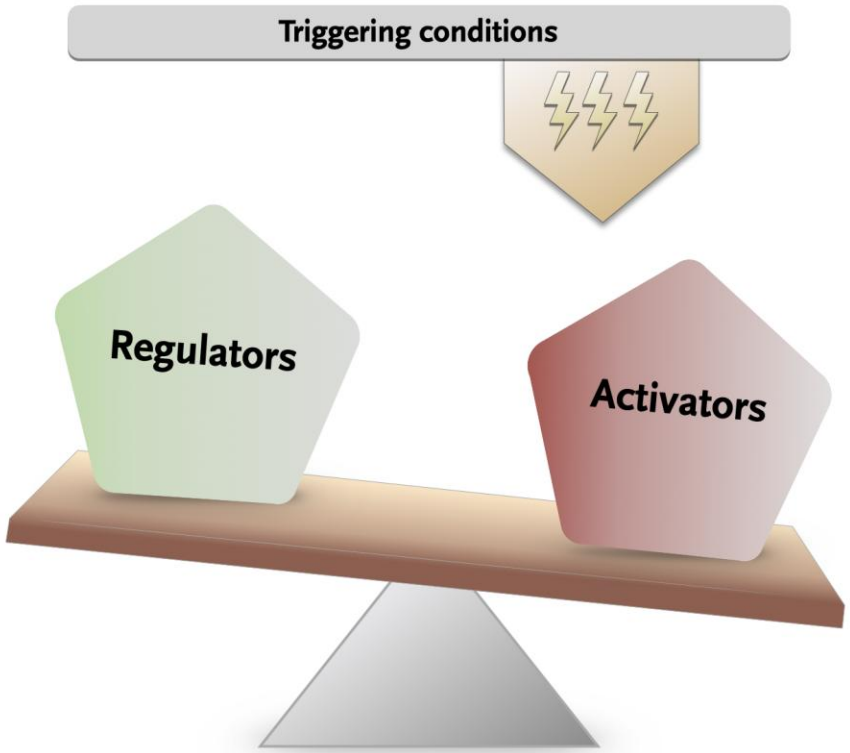
Introduction

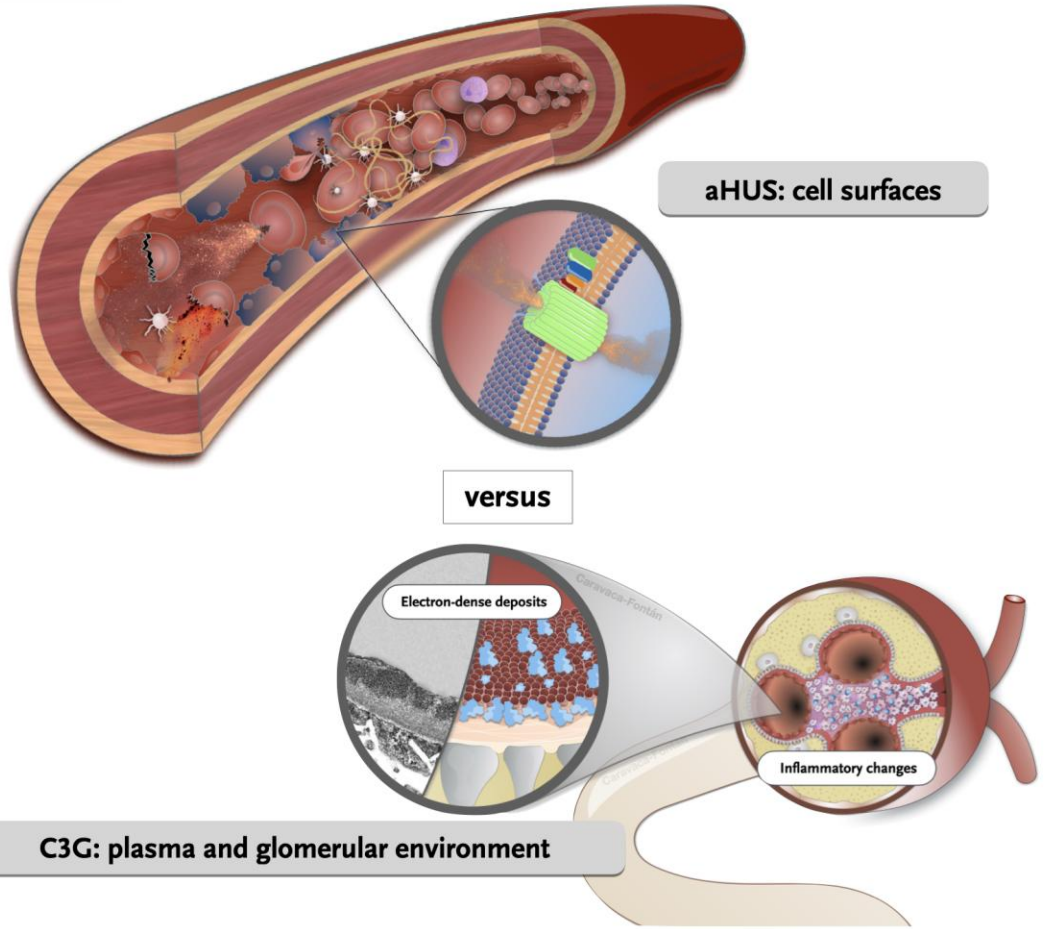




C3 Glomerulopathy and Primary IC-MPGN

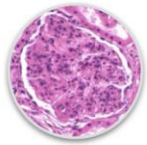
Introduction



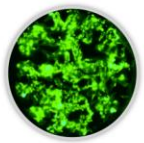


C3 Glomerulopathy and Primary IC-MPGN

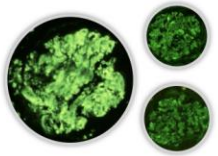
Definition



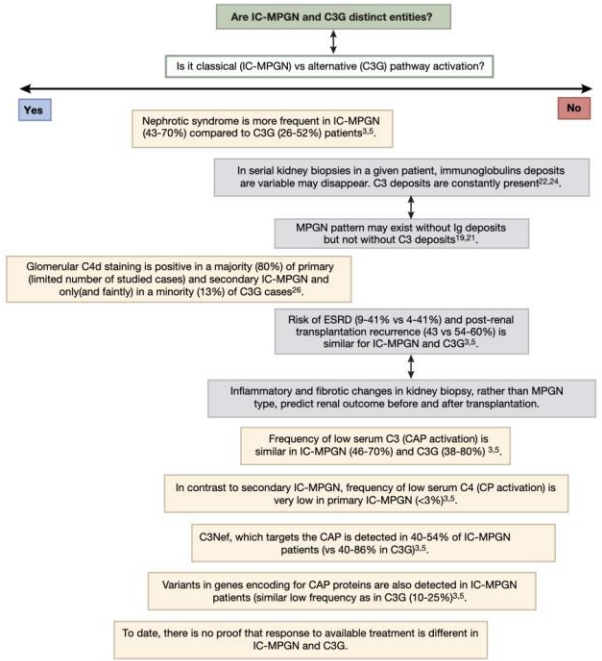
Primary IC–MPGN

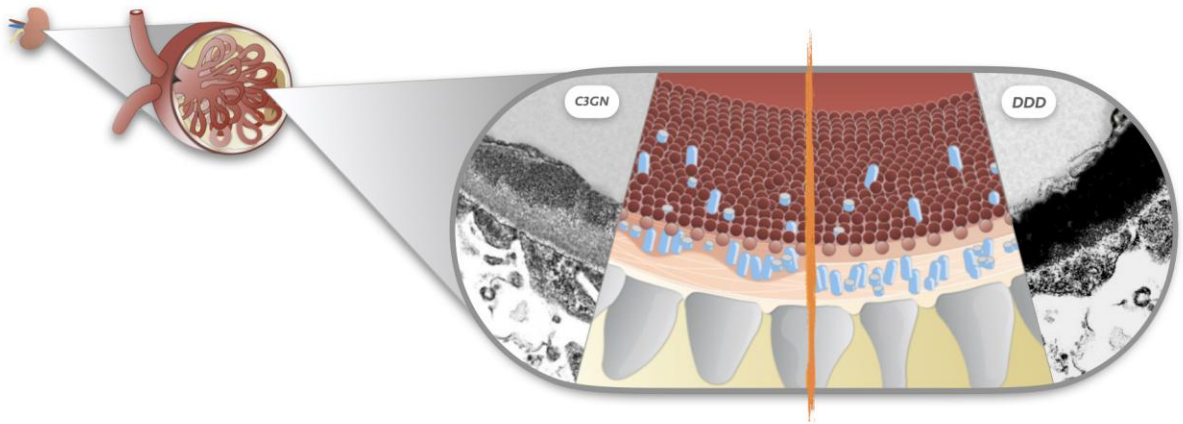


Exclusive



C3 dominant

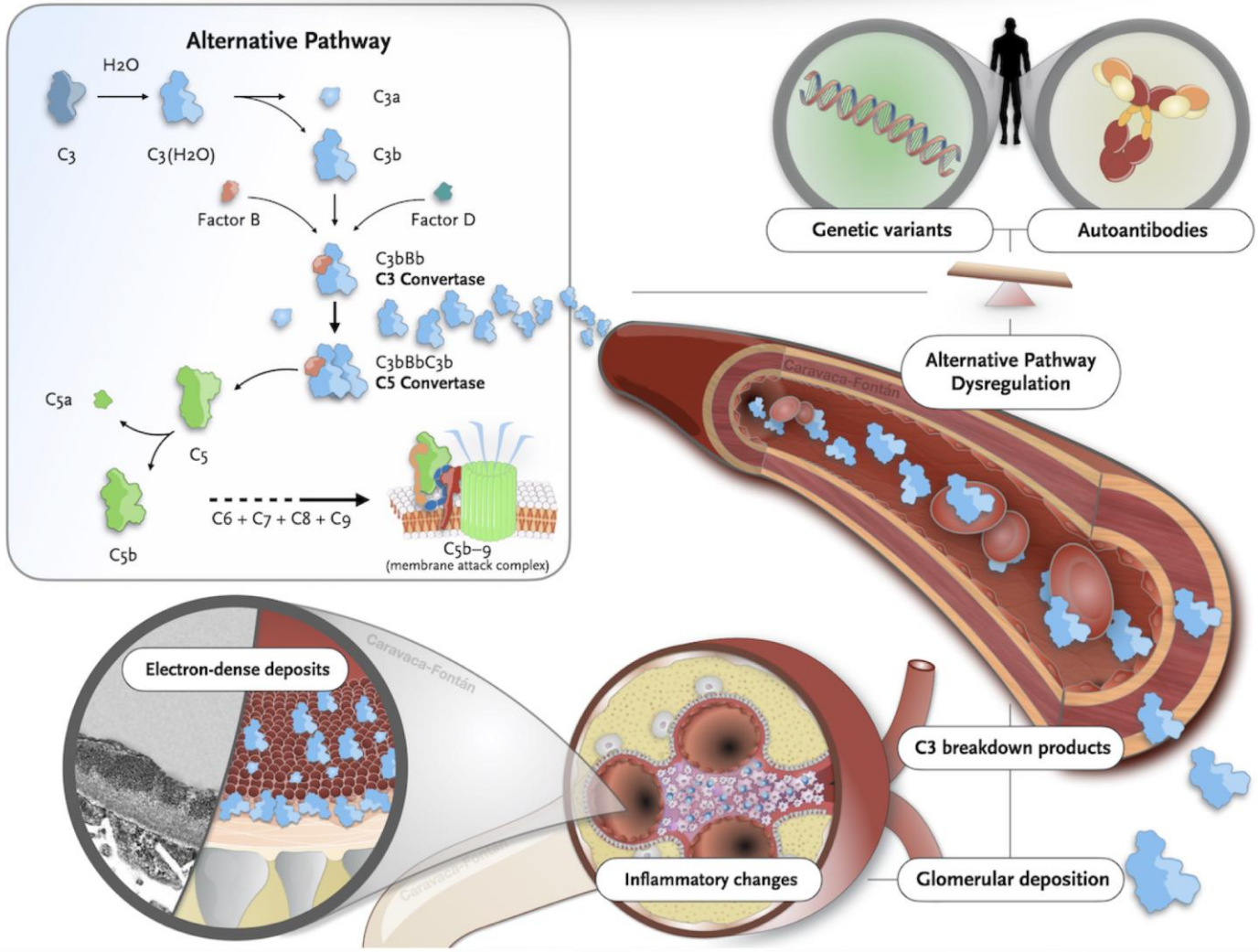




- ***Immunofluorescence staining results may vary, leading to potential misdiagnosis. Subsequent kidney biopsy may reveal findings consistent with IC-MPGN or C3G***
- ***Genetic variants or autoantibodies are found in similar proportions in both C3G and primary IC-MPGN, suggesting they may represent two histologic phenotypes of the same condition.***

C3 Glomerulopathy and Primary IC-MPGN

Pathogenesis



C3 Glomerulopathy and Primary IC-MPGN

Pathogenesis

- **Loss of function pathogenic variants in regulatory proteins**
  - CFH, CFI
- **Gain of function pathogenic variants in pathway proteins**
  - CFB, C3
- **CNVs in CFHR locus**
  - Rearrangements (i.e., CFH-CFHR1 or CFHR3-CFHR4 fusion proteins)
  - Large deletions (i.e., CFH-CFHR1-CFHR3)
  - Exonic duplication in CFHR51

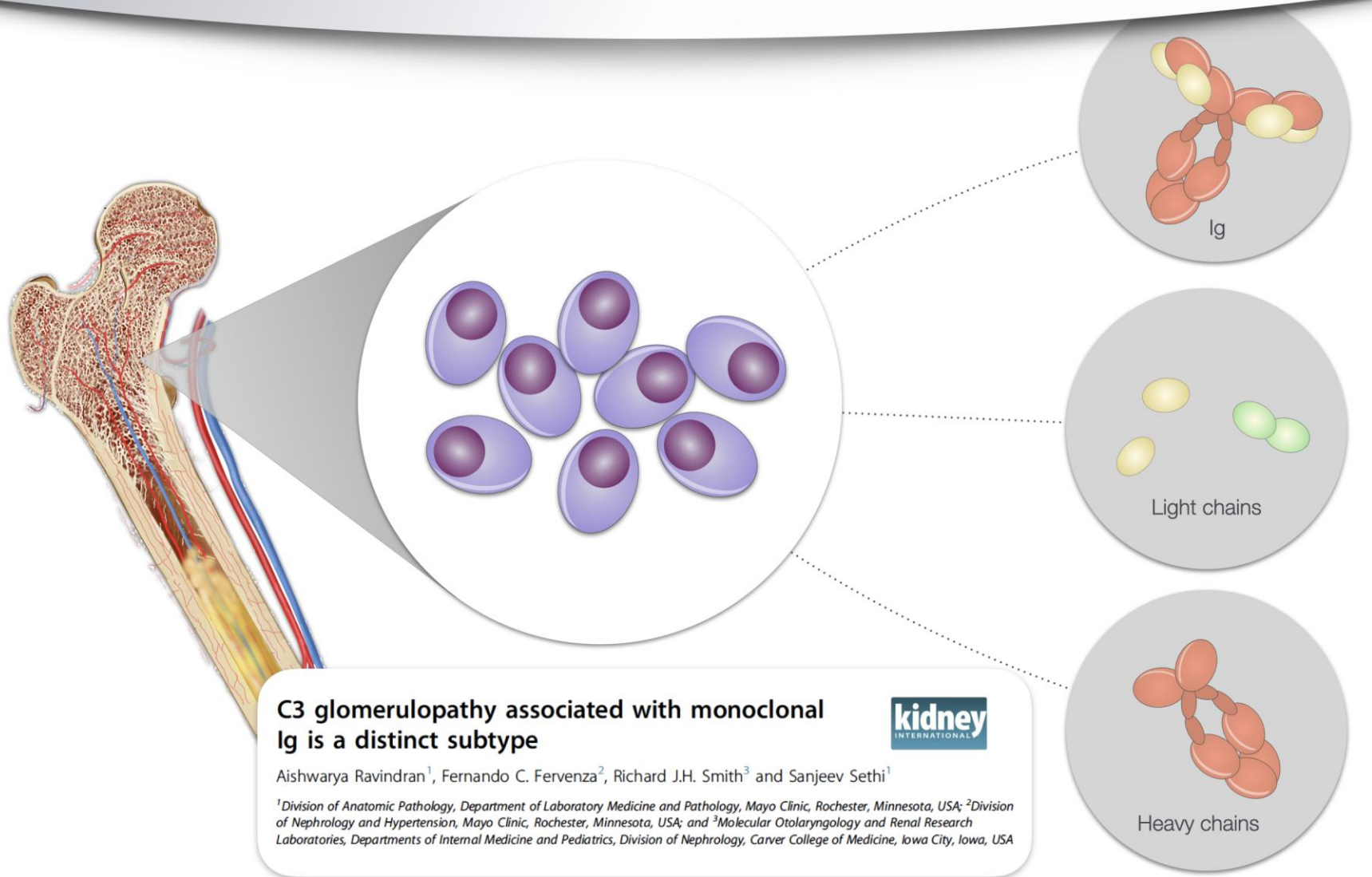
C3 Glomerulopathy and Primary IC-MPGN

Pathogenesis

- Nephritic factors
- Anti-FH
- Anti-FB

C3 Glomerulopathy and Primary IC-MPGN

Pathogenesis



C3 glomerulopathy associated with monoclonal Ig is a distinct subtype

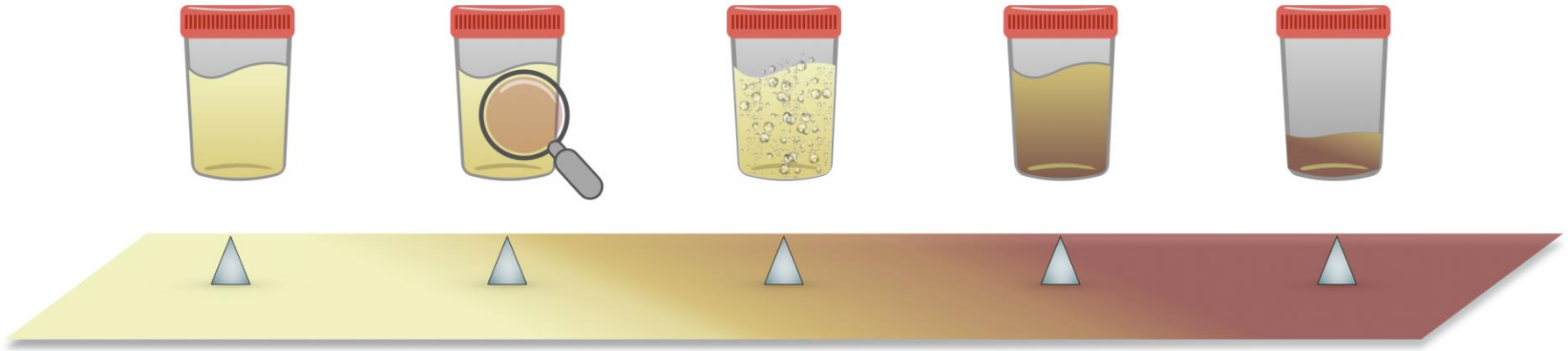
kidney INTERNATIONAL

Aishwarya Ravindran[1], Fernando C. Fervenza[2], Richard J.H. Smith[3] and Sanjeev Sethi[1]

[1]Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA; [2]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; and [3]Molecular Otolaryngology and Renal Research Laboratories, Departments of Internal Medicine and Pediatrics, Division of Nephrology, Carver College of Medicine, Iowa City, Iowa, USA

C3 Glomerulopathy and Primary IC-MPGN

Disease onset



Asymptomatic urinary abnormalities

Microscopic hematuria

Nephrotic syndrome

Nephritic syndrome

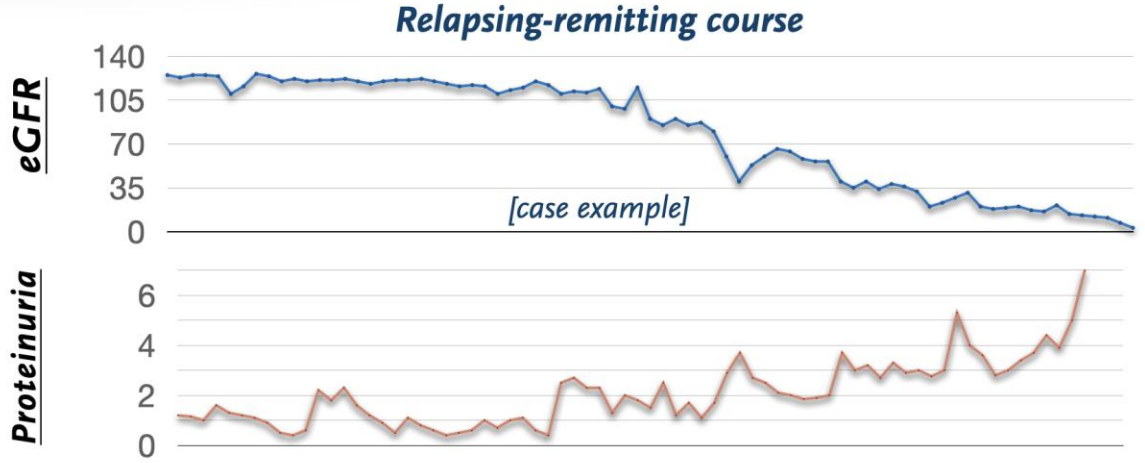
Rapidly progressive kidney failure

Low serum C3 in up to 50%

C3 Glomerulopathy and Primary IC-MPGN

Natural History and Prognosis

- ***High heterogeneity*** *(age at diagnosis, form of presentation, underlying pathogenesis...).*
- ***Retrospective bias of previous cohorts*** *(treatments received, therapeutic decisions...).*



30–50%

Eventually progress within 10 years, requiring dialysis or transplantation

C3 Glomerulopathy and Primary IC-MPGN

Natural History and Prognosis

Prognostication for C3 Glomerulopathy and Idiopathic Immunoglobulin-Associated Membranoproliferative Glomerulonephritis.

Fernando Caravaca-Fontán[1] *and Manuel Praga*[1,2]

CJASN

Table 1. Summary of the main C3 glomerulopathy/Ig-mediated membranoproliferative GN cohort studies with the clinical and histologic parameters associated with outcomes in unadjusted or multivariable analyses

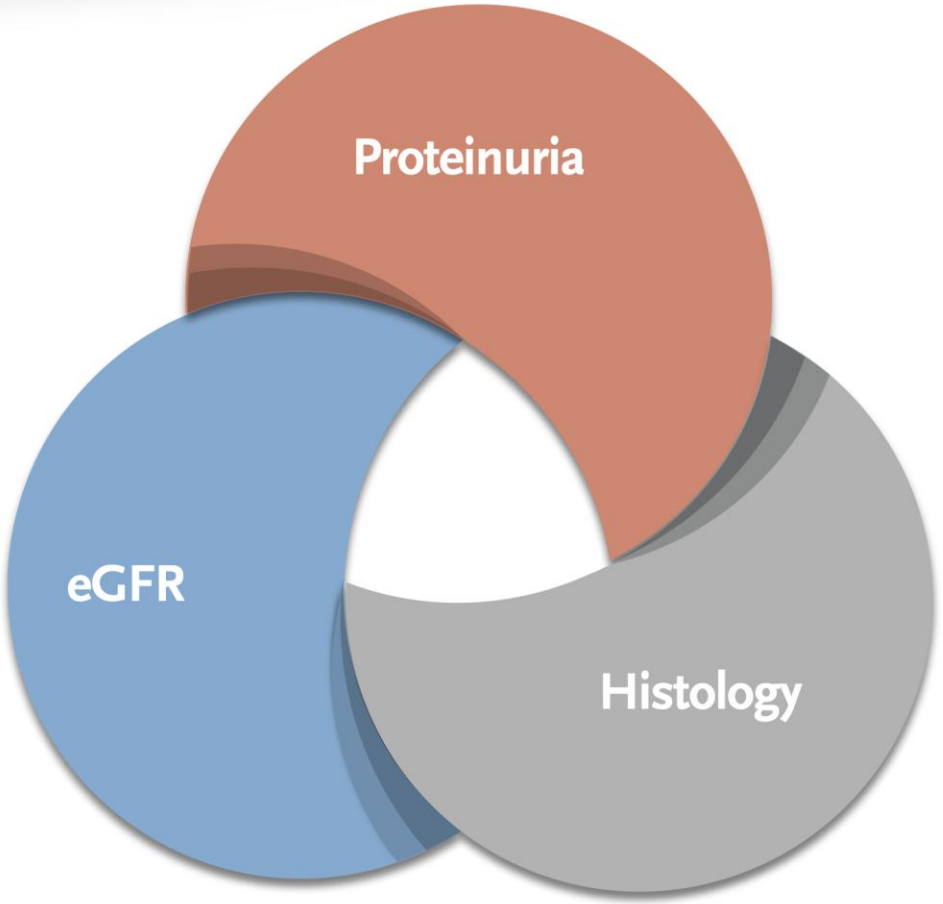
Reference	Patients	Outcomes	Clinical Covariates	Histologic Parameters
Servais *et al.* (9) (2012)	C3 GN (n=56), DDD (n=29), Ig-MPGN (n=49)	Kidney failure	eGFR; age; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	—
Medjeral-Thomas *et al.* (10) (2014)	C3 GN (n=59), DDD (n=21)	Kidney failure	Age; SCr	Crescentic GN; DDD
Caliskan *et al.* (11) (2017)	C3 GN (n=59), DDD (n=7)	Kidney failure or eGFR decline ≥50% from the baseline	Age; eGFR; proteinuria; no remission of proteinuria	Percentage of crescents; percentage of sclerotic glomeruli; severity of interstitial fibrosis
Bomback *et al.* (4) (2018)	C3 GN (n=87), DDD (n=24)	Doubling of SCr or kidney failure	eGFR	Interstitial fibrosis/tubular atrophy; total activity score; total chronicity score
Ravindran *et al.* (5) (2018)	C3 GN (n=102), DDD (n=12)	Doubling of SCr or kidney failure	SCr; proteinuria	Global glomerulosclerosis; interstitial fibrosis/ tubular atrophy
Caravaca-Fontán *et al.* (3) (2020)	C3 GN (n=81), DDD (n=16)	Disease remission; kidney failure	Sex; age; proteinuria; MMF treatment; eGFR	—; interstitial fibrosis/ tubular atrophy
Khandelwal *et al.* (12) (2020)[a]	C3 GN (n=26), DDD (n=48), Ig-MPGN (n=18)	Disease remission; kidney failure	Serum albumin; low C3; age; eGFR; rapid progression	— ; DDD; interstitial fibrosis/tubular atrophy
Wong *et al.* (13) (2021)[a]	C3 GN (n=25), DDD (n=14), Ig-MPGN (n=31), IC GN (n=10)	Kidney failure	—	Presence of >50% crescent
Lomax-Browne *et al.* (6) (2022)	C3 GN (n=106), DDD (n=17), Ig-MPGN (n=33)	Doubling of SCr or kidney failure	eGFR; proteinuria	Interstitial fibrosis/tubular atrophy; cellular/ fibrocellular crescents

DDD, dense deposit disease; Ig-MPGN, Ig-mediated membranoproliferative GN; —, no data; SCr, serum creatinine; MMF, mycophenolate mofetil; IC, immune complex.
[a]Pediatric patients.

C3 Glomerulopathy and Primary IC-MPGN

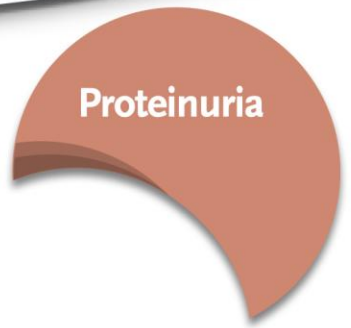
Surrogate markers of outcomes

- ✓ *Kidney failure is a late event in the progression of the disease.*
- ✓ *The use of surrogate endpoints to predict clinically relevant events and to investigate the potential effectiveness of new therapeutic strategies, become compulsory.*



C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes



Comparative Analysis of Proteinuria and Longitudinal Outcomes in Immune Complex Membranoproliferative Glomerulonephritis and C3 Glomerulopathy

KI REPORTS
KIReports.org

Fernando Caravaca-Fontán[1], Remedios Toledo-Rojas[2], Ana Huerta[3], José Luis Pérez-Canga[4], Patricia Martínez-Miguel[5], Rosa Miquel[6], Iara Da Silva[7], Úrsula Verdalles[8], Macarena Albornoz[3], Carmen Mercedes Durán López[5], Carmen Mon[9], Gema Fernández-Juárez[10] and Manuel Praga[11]; on behalf of the C3G study group from the Spanish Group for the Study of Glomerular Diseases[12]

- The study included 149 patients: 98 with C3G (66%) and 51 with IC-MPGN (34%)
- During a median follow-up of 65 (IQR: 32–114) months, 44 patients (30%) progressed to kidney failure without differences across C3G or IC-MPGN.
- Hypothesis: *An early change in proteinuria could help predict the prognosis of the disease, and this information could be relevant to evaluate the effectiveness of experimental treatments*

C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes

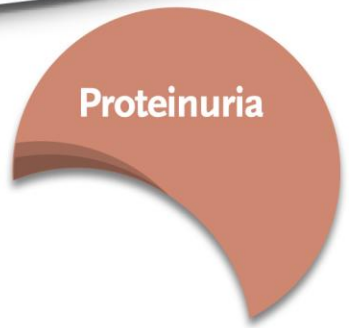


Table 2. Joint model showing the association between the longitudinal change in proteinuria and the hazard of kidney failure

Model	Hazard ratio	95% confidence interval	*P*-value
Linear mixed submodel			
Intercept	2.50	2.19–2.88	<0.001
Time, mo	0.54	0.42–0.69	<0.001
Cox regression submodel			
Age			0.17
Pediatric	1.00 (reference)	1.00 (reference)	
Adult	0.31	0.06–1.63	
Gender			0.52
Female	1.00 (reference)	1.00 (reference)	
Male	0.76	0.31–1.75	
Baseline eGFR			<0.001
< 60	1.00 (reference)	1.00 (reference)	
≥ 60	0.06	0.01–0.25	
Histologic subtype			0.47
Dense deposit disease	1.00 (reference)	1.00 (reference)	
C3 glomerulonephritis	0.32	0.09–1.17	
IC-MPGN	0.92	0.27–3.16	
Total activity score			0.62
< 9	1.00 (reference)	1.00 (reference)	
≥ 9	1.22	0.54–2.58	
Total chronicity score			<0.001
< 4	1.00 (reference)	1.00 (reference)	
≥ 4	8.96	3.94–20.4	
Joint model			
Longitudinal change in proteinuria (per g/d increment)	3.18	1.95–5.83	<0.001

eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis.

Table 3. Joint model showing the association between a 50% reduction in proteinuria during follow-up time, and the hazard of kidney failure

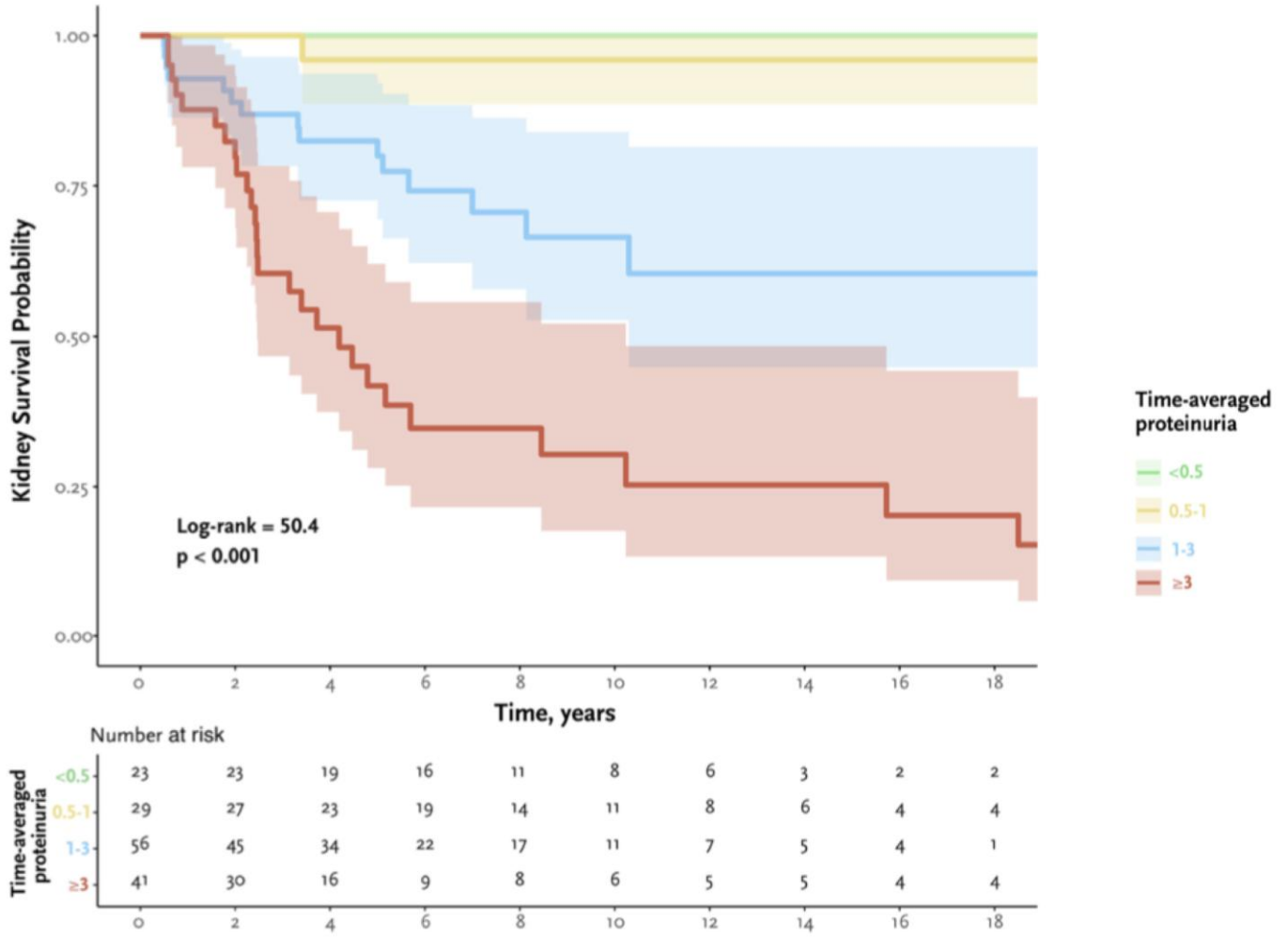
Model	Hazard ratio	95% confidence interval	*P*-value
Linear mixed submodel			
Intercept	0.21	0.14–0.30	<0.001
Time, mo	1.08	1.06–1.09	<0.001
Cox regression submodel			
Age			0.97
Pediatric	1.00 (reference)	1.00 (reference)	
Adult	1.04	0.35–3.37	
Gender			0.71
Female	1.00 (reference)	1.00 (reference)	
Male	1.15	0.56–2.35	
Baseline eGFR			<0.001
< 60	1.00 (reference)	1.00 (reference)	
≥ 60	0.12	0.04–0.34	
Histologic subtype			0.37
Dense deposit disease	1.00 (reference)	1.00 (reference)	
C3 glomerulonephritis	0.39	0.14–1.13	
IC-MPGN	0.83	0.31–2.21	
Total activity score			0.85
< 9	1.00 (reference)	1.00 (reference)	
≥ 9	0.92	0.43–1.91	
Total chronicity score			<0.001
< 4	1.00 (reference)	1.00 (reference)	
≥ 4	7.51	3.24–13.4	
Joint model			
≥ 50% proteinuria reduction	0.61	0.46–0.75	<0.001

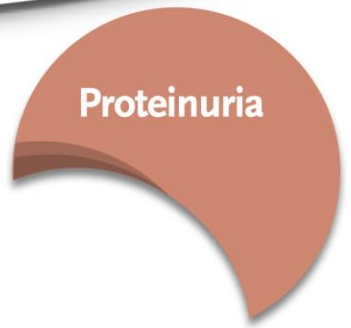
eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis.

- ***Longitudinal changes in proteinuria were strongly associated with the risk of reaching kidney failure***
- ***A ≥50% proteinuria reduction over follow-up time was significantly associated with a lower risk of kidney failure***

C3 Glomerulopathy and Primary IC-MPGN

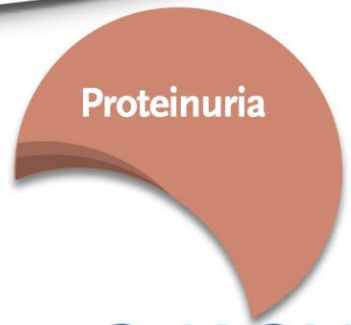
Surrogate markers of outcomes





C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes



Clinical and histologic predictors of kidney outcomes in C3 glomerulopathy and idiopathic MPGN

CJASN
Clinical Journal of the American Society of Nephrology
Clinical Research

225 patients with C3 glomerulopathy (C3G) or idiopathic immune complex membranoproliferative glomerulonephritis IC-MPGN

From 3 international centers

Evaluated the association between clinical and histologic variables and composite outcome of 30% decline in eGFR or ESKD
Using Cox proportional hazards models

Prediction model derived and internally validated through bootstrap resampling

Lower eGFR, paraprotein presence, and interstitial fibrosis associated with a higher outcome risk

Native disease (versus recurrence post-transplantation), White ethnicity, and lower C4 levels associated with lower risk

Prediction model including these variables performed well
R^2_D: *53.14%, C-statistic 0.84 (95% CI 0.82-086), integrated calibration index: 0.31*

Model retained robustness after internal validation

50% reduction in proteinuria from baseline to a value of < 1g/day associated with lower risk of outcome independent of other risk factors
HR 0.35, 95% CI 0.12-0.97

Conclusions: Our study evaluated the baseline clinical and histologic parameters associated with renal outcome using the largest C3G/idiopathic IC-MPGN cohort to date. These factors were included in a prediction model to assess individual patient risk. Our results provide an evidence-based definition of proteinuria remission that can be used for patient care and in clinical trials.

Malak Ghaddar, Fernando Caravaca-Fontán, Manual Praga, et al. ***Clinical and histologic predictors of kidney outcomes in C3 glomerulopathy and idiopathic MPGN.*** CJASN DOI: 10.2215/CJN.0000000751
Visual Abstract by AC Gomez, MD

Primary C3 glomerulopathy and Immunocomplex-mediated membranoproliferative glomerulonephritis: natural history and clinical predictors of long-term kidney outcomes

CJASN
Clinical Journal of the American Society of Nephrology
Clinical Research

Retrospective study

Italian Registry of MPGN

Patients with biopsy proven primary MPGN

Demographic, clinical and biological parameters collected

Composite outcomes
- ESKD
- Doubling of serum creatinine
- Death from kidney causes

IC-MPGN: 40%
C3G: 60%
- **C3GN:** 67%
- **DDD:** 19%

Study population
- Female 41%
- **Median age:** 15 years
- **Median eGFR:** 83 ml/min/1.73m²

Clinical presentation:
- Hematuria: **85%**
- Nephrotic-range proteinuria: **45%**
IC-MPGN: 58%

Complement studies:
C3: **84%**
C4: **30%**
sC5b-9 C3GN
C3NeFs DDD

Each gram ↑ in 1-year of proteinuria levels
↑ **33%** risk of progression
Kidney survival in patients with **1-year proteinuria <1 g/24h**

↑ **eGFR**
At 1-year **inversely associated** with composite endpoint [HR 0.97, 95% IC, 0.95-1]
eGFR at 1 year in patients who reached the composite endpoint

ESKD progression:
26%
5 years follow-up from diagnosis

10-year ESKD-free survival
Pediatric onset
<12 years **86%**
Adolescence **78%**
*Independent of the histological category

Complement dysregulation and rare genetic variants **did not predict outcomes**

Conclusions: Results from a large and well-characterized cohort of individuals with primary C3G/IC-MPGN identify age at onset and proteinuria levels as a key predictors for kidney survival.

Giliane Nanchen, Maddalena Marasà, Matteo Breno, et al. **Primary C3 glomerulopathy and Immunocomplex-mediated membranoproliferative glomerulonephritis: natural history and clinical predictors of long-term kidney outcomes.** CJASN, DOI: DOI: 10.2215/CJN.0000000953
Visual Abstract by Maria Fernanda Zavala, MD, MSc

C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes

- Patients progress through declining levels of eGFR before reaching kidney failure.
- As such, clinically significant treatment effects on the loss of kidney function as measured by eGFR would be expected to predict treatment effects on progression to kidney failure.
- Analysis of outcomes in C3G in the Rare Kidney Disease Registry demonstrates a consistent association of annualized 24-month slope of eGFR with HR of kidney failure over a 20-year period. For example, the kidney failure HR for –6 ml/min per 1.73 m2 per year compared with stable eGFR was 1.61 (95% CI, 1.11 to 2.32).

C3 Glomerulopathy and Primary IC-MPGN

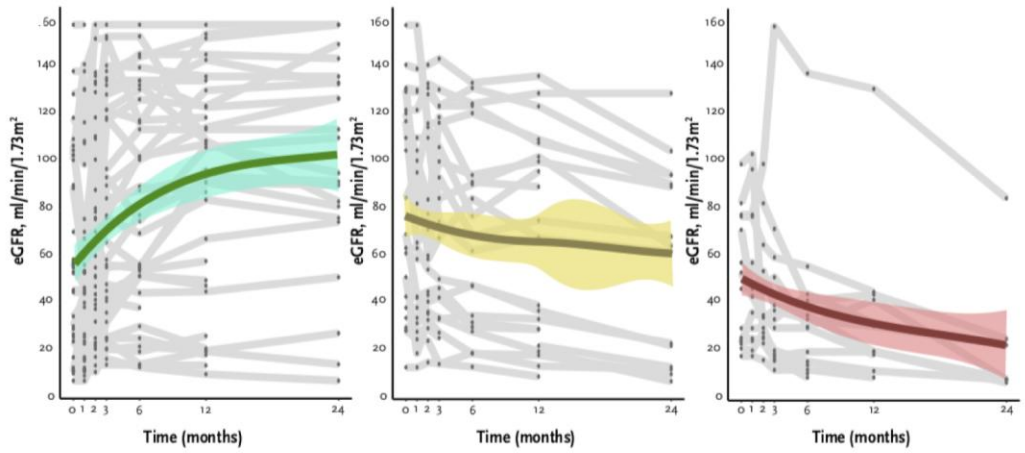
Surrogate markers of outcomes

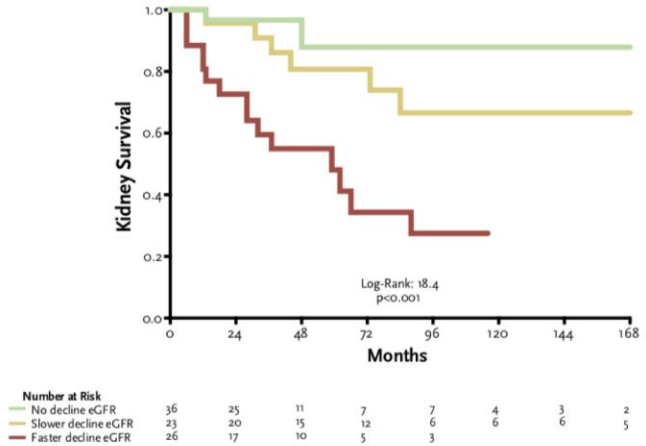
eGFR

Clinical Profiles and Patterns of Kidney Disease Progression in C3 Glomerulopathy

Kidney360

Fernando Caravaca-Fontán,[1,2] Teresa Cavero,[3] Montserrat Díaz-Encarnación,[4] Virginia Cabello,[5] Gema Ariceta,[6] Luis F. Quintana,[7] Helena Marco,[8,9] Xoana Barros,[10] Natalia Ramos,[11] Nuria Rodríguez-Mendiola,[12] Sonia Cruz,[13] Gema Fernández-Juárez,[14,15] Adela Rodríguez,[16] Ana Pérez de José,[17] Cristina Rabasco,[18] Raquel Rodado,[19] Loreto Fernández,[20] Vanessa Pérez-Gómez,[21] Ana Ávila,[22] Luis Bravo,[23] Natalia Espinosa,[24] Natalia Allende,[25] Maria Dolores Sanchez de la Nieta,[26] Eva Rodríguez,[27] Begoña Rivas,[28] Marta Melgosa,[29] Ana Huerta,[30] Rosa Miquel,[31] Carmen Mon,[32] Gloria Fraga,[33] Alberto de Lorenzo,[34] Juliana Draibe,[35] Fayna González,[36] Amir Shabaka,[37] Maria Esperanza López-Rubio,[38] María Ángeles Fenollosa,[39] Luis Martín-Penagos,[40] Iara Da Silva,[4,41] Juana Alonso Titos,[42] Santiago Rodríguez de Córdoba,[43] Elena Goicoechea de Jorge,[1,44] and Manuel Praga,[1,2,3] on behalf of the Spanish Group for the Study of Glomerular Diseases (GLOSEN)





C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes

Histology

C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy

kidney INTERNATIONAL

Andrew S. Bomback[1], Dominick Santoriello[2], Rupali S. Avasare[3], Renu Regunathan-Shenk[1], Pietro A. Canetta[1], Wooin Ahn[1], Jai Radhakrishnan[1], Maddalena Marasa[1], Paul E. Rosenstiel[2], Leal C. Herlitz[4], Glen S. Markowitz[2], Vivette D. D'Agati[2] and Gerald B. Appel[1]

C3 Glomerulopathy Histopathologic Index

Activity Score (0–21)	*Chronicity Score (0–10)*
Mesangial hypercellularity	Glomerulosclerosis
Endocapillary proliferation	Tubular atrophy
MPGN pattern	Interstitial fibrosis
Leukocyte infiltration	Arterio- and arteriolosclerosis
Crescents formation	
Fibrinoid Necrosis	
Interstitial inflammation	

C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes

Histology

C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy

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C3 Glomerulopathy Histopathologic Index

- **Multivariable analysis**: Both **Total Activity Score** and **Total Chronicity Score** emerged as independent predictors of worse kidney outcomes.

C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes

Histology

Validation of a Histologic Scoring Index in C3 Glomerulopathy

Fernando Caravaca-Fontán, Hernando Trujillo, Marina Alonso, Montserrat Díaz-Encarnación, Virginia Cabello, Gema Ariceta, Luis F. Quintana, Helena Marco, Xoana Barros, Natalia Ramos, Nuria Rodríguez-Mendiola, Sonia Cruz, Gema Fernández-Juárez, Eva Rodríguez, Francisco de la Cerda, Ana Pérez de José, Inmaculada López, Loreto Fernández, Vanessa Pérez Gómez, Ana Ávila, Luis Bravo, Javier Lumbreras, Natalia Allende, Maria Dolores Sanchez de la Nieta, Teresa Olea, Marta Melgosa, Ana Huerta, Rosa Miquel, Carmen Mon, Gloria Fraga, Alberto de Lorenzo, Juliana Draibe, Fayna González, Amir Shabaka, Maria Luisa Illescas, Consuelo Calvo, Victoria Oviedo, Iara Da Silva, Elena Goicoechea de Jorge, Francisco Caravaca, and Manuel Praga, on behalf of the C3G Study Group of the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

AJKD

- **Aim:** To evaluate the reproducibility of C3G Histologic Index previously proposed by Columbia University, and to analyze its prognostic value.

C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes

Histology

Validation of a Histologic Scoring Index in C3 Glomerulopathy

AJKD

C3 Glomerulopathy Histopathologic Index

Activity Score (0–21)	*Chronicity Score (0–10)*
Mesangial hypercellularity	Glomerulosclerosis
Endocapillary proliferation	Tubular atrophy
MPGN pattern	Interstitial fibrosis
Leukocyte infiltration	Arterio- and arteriolosclerosis
Crescents formation	
Fibrinoid Necrosis	
Interstitial inflammation	

C3 Glomerulopathy and Primary IC-MPGN

Surrogate markers of outcomes

Histology

Validation of a Histologic Scoring Index in C3 Glomerulopathy

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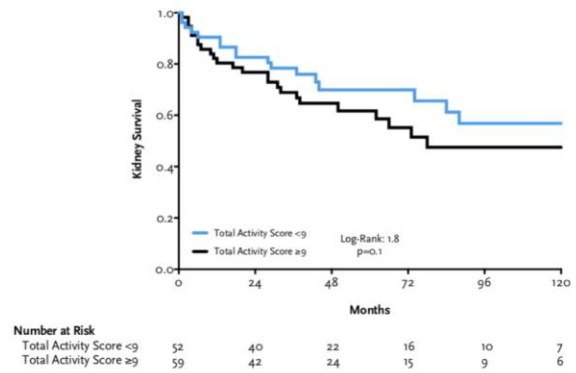
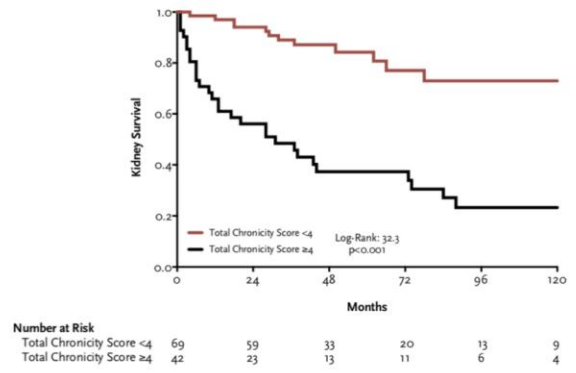
C3G-HI model				
Total Activity Score		0.06		0.15
<9	1.00 (reference)		1.00 (reference)	
≥9	1.16 (0.94-1.29)		1.41 (0.87-2.15)	
Total Chronicity Score		<0.001		<0.001
<4	1.00 (reference)		1.00 (reference)	
≥4	4.43 (2.28-6.54)		5.16 (2.74-9.72)	

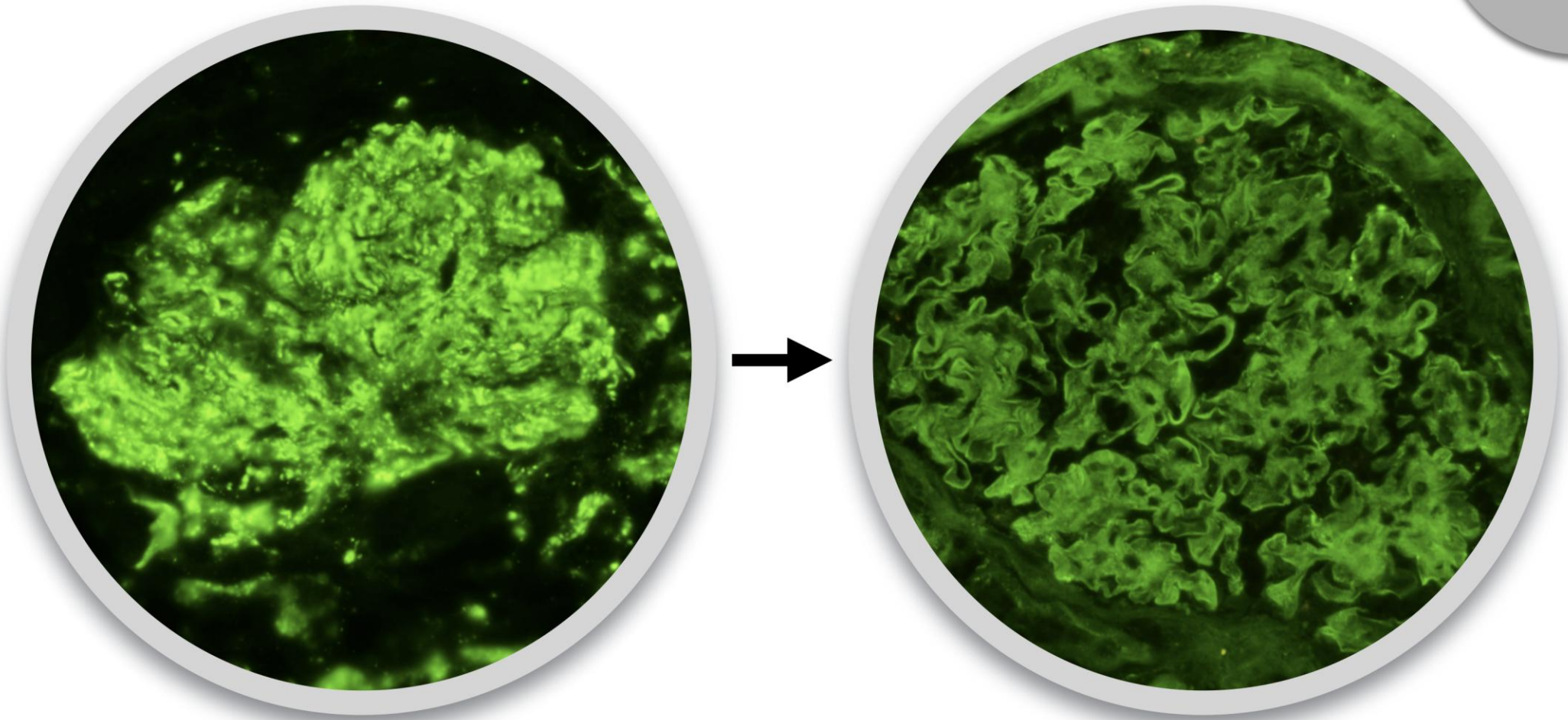




C3 Glomerulopathy and Primary IC-MPGN

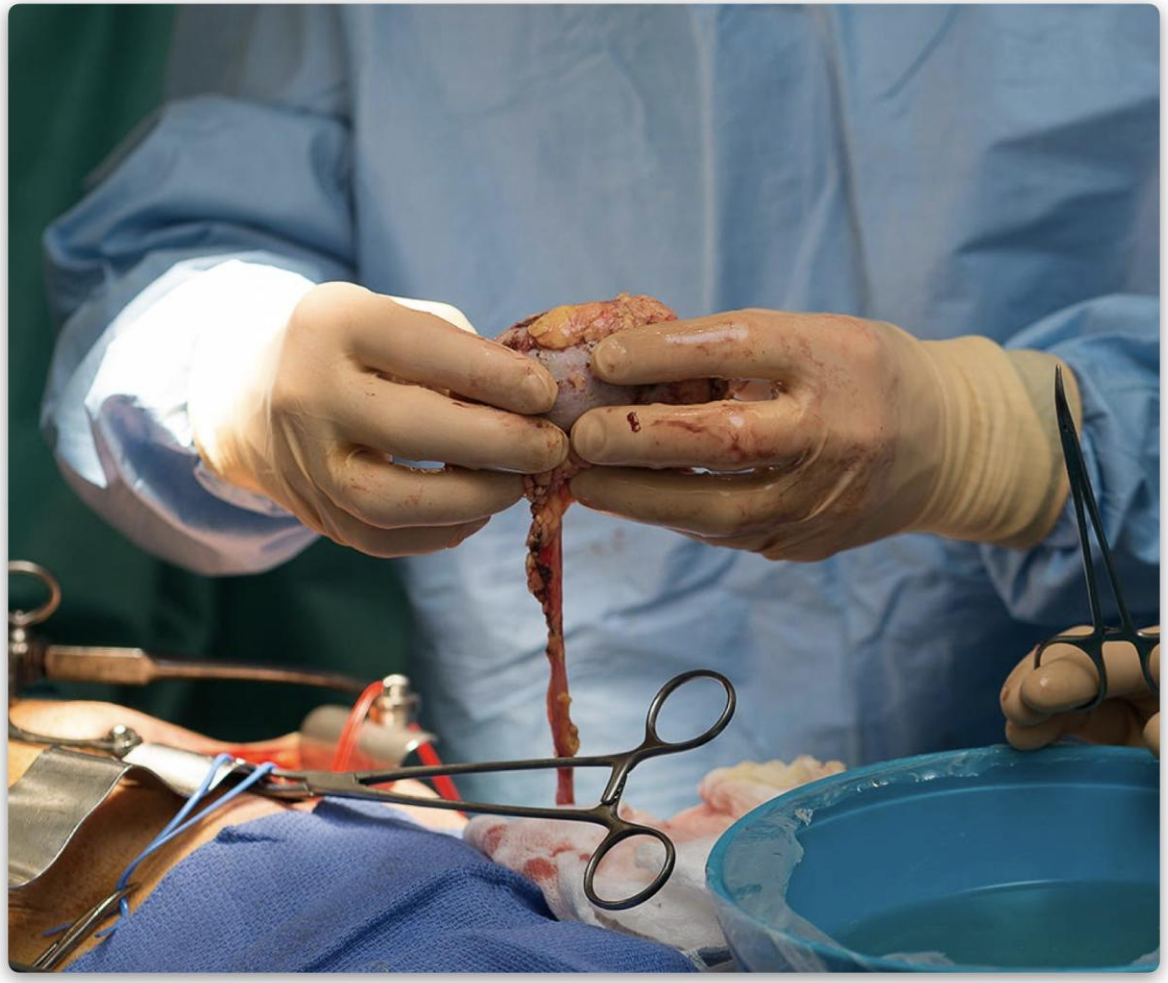
Surrogate markers of outcomes

Histology



C3 Glomerulopathy and Primary IC-MPGN

Recurrence risk in kidney transplantation



≥ 50%

May eventually develop disease recurrence in the allograft

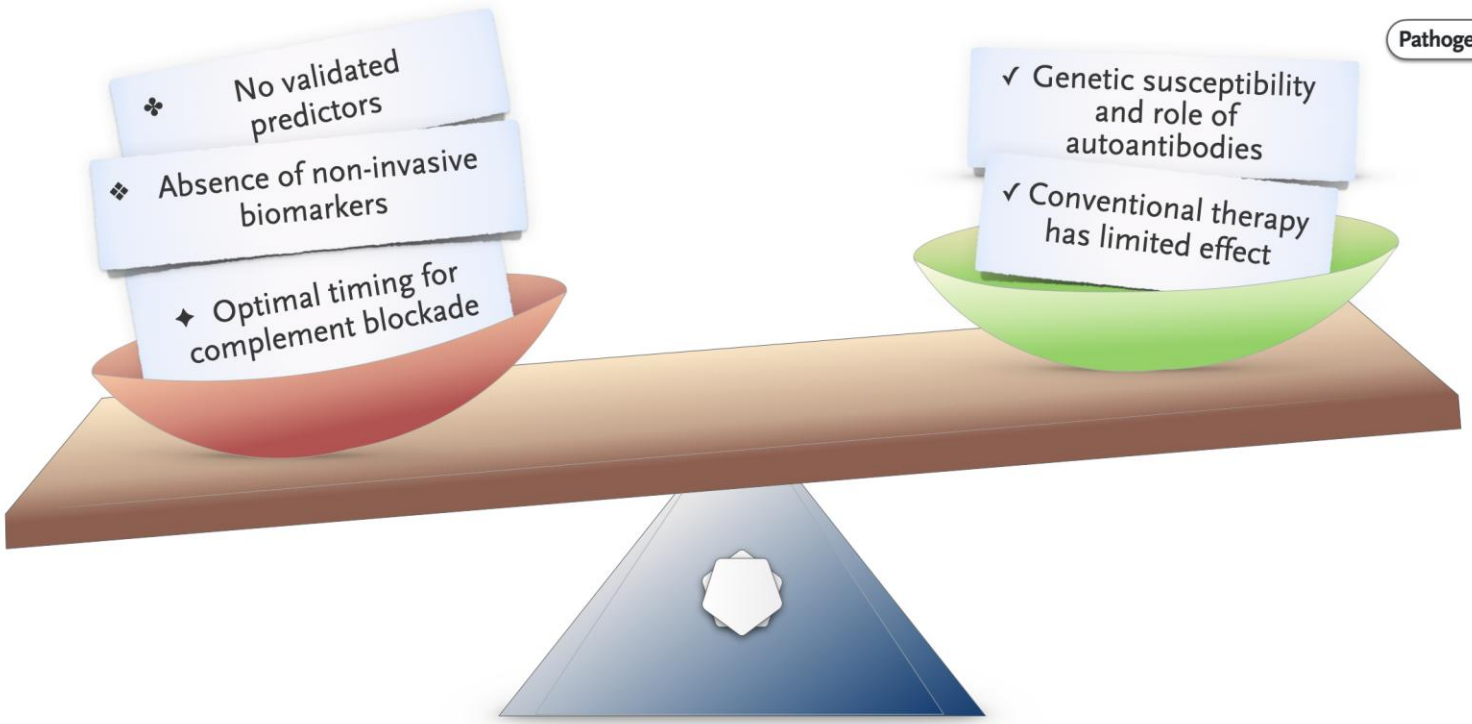
≥50%

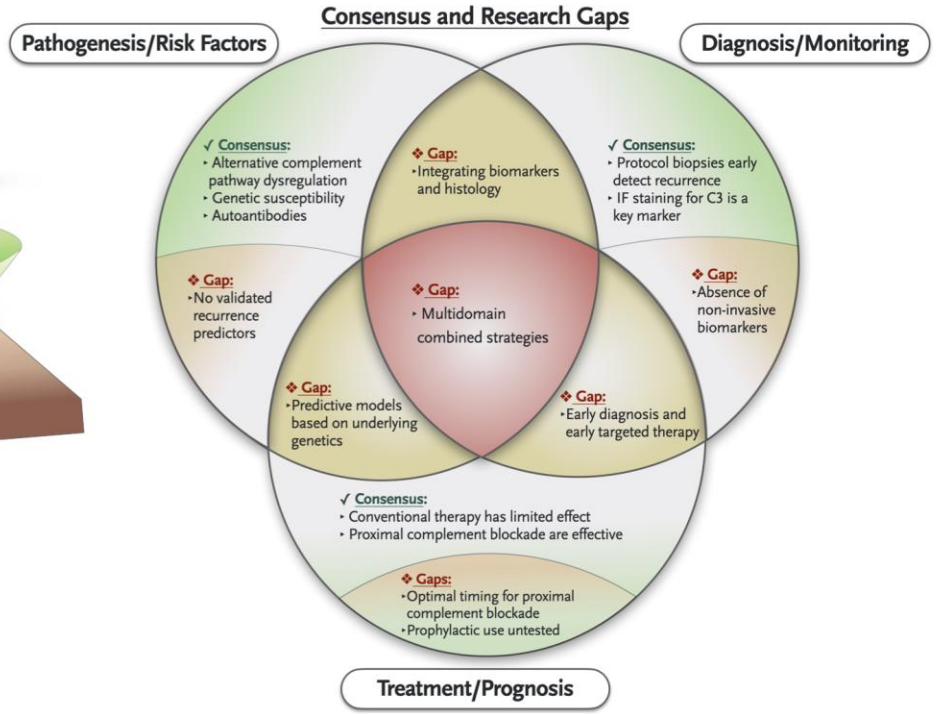
May suffer graft loss

C3 Glomerulopathy and Primary IC-MPGN

Recurrence risk in kidney transplantation

➡ ***At present, uncertainties outweigh established evidence.***





C3 Glomerulopathy and Primary IC-MPGN

Recurrence risk in kidney transplantation

➡ ***Old studies identified the following predictors of recurrence:***

1. Living donor transplantation may carry a higher recurrence risk, possibly due to shared genetics or active disease at the time of preemptive transplantation, though evidence is inconsistent.
2. Triggers for recurrence: infections and ischemia–reperfusion injury (especially with prolonged cold ischemia), which can activate the alternative complement pathway.
3. Young age at kidney transplantation
4. High proteinuria and low serum C_3 levels
5. Severe histological lesions, such as mesangial proliferation or crescents

✓ *However, studies were from periods when C3G was not a recognized entity.*

C3 Glomerulopathy and Primary IC-MPGN

Recurrence risk in kidney transplantation

What are the clinical and histopathological features of C3 glomerulopathy recurring after kidney transplantation?

CJASN
Clinical Journal of the American Society of Nephrology

Retrospective study
2016 – 2023

18 kidney transplant recipients with native kidney failure attributed to C3 glomerulopathy (C3G)

- **12 with C3 glomerulo-nephritis** (C3GN)
- **6 with dense deposit disease** (DDD)

Median follow-up
37 months

Characteristics of C3G recurrence post-transplantation

Recurrence rates & timing	**89%** **at 33 (13, 141) days post-transplantation** **38%** detected via protocol biopsies **62%** detected via biopsies performed for clinical causes
Immuno-fluorescence	**Granular glomerular C3 staining in all cases** 2+ median intensity, 50% C3-only and 50% C3-dominant
Electron microscopy	**Electron-dense deposits in all cases** 88% mesangial, 38% subepithelial, 12% subendothelial Similar deposits in C3GN and DDD
Clinical outcomes	**Functional grafts in all cases at follow-up** Median eGFR 53 ml/min/1.73 m^2

Conclusions: Most patients with native kidney failure attributed to C3G developed disease recurrence very early after kidney transplantation. Immunofluorescence and electron microscopy played a crucial role in detecting early, sub-clinical recurrence of C3GN and DDD.

Blanca Tarragón, Yonatan Peleg, Geetha Jagannathan et al. **C3 Glomerulopathy Recurs Early after Kidney Transplantation in Serial Biopsies Performed within the First Two Years Post-Transplantation.** 2024, CJASN DOI: 10.2215/CJN.0000000000000474 **Visual Abstract by Corina-Gabriela Teodosiu, MD**

C3 Glomerulopathy and Primary IC-MPGN

Recurrence risk in kidney transplantation

➡ ***Despite all these advances, significant knowledge gaps remain:***

- ✓ ***The natural history of recurrent C3G and IC-MPGN post-transplant is poorly characterized due to limited high-quality, longitudinal data.***
- ✓ ***Reliable predictors of recurrence are lacking and the role of acquired complement autoantibodies remains unclear***
- ✓ ***The importance of surrogate markers of outcomes (e.g. eGFR slope and proteinuria) are unclear.***

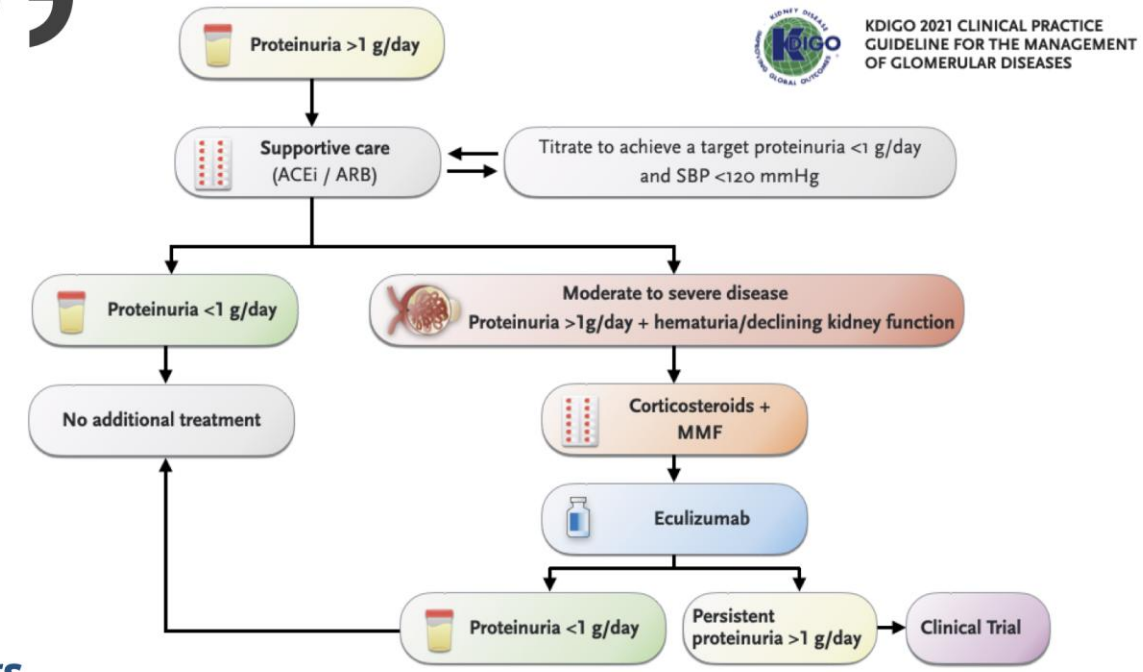
C3 Glomerulopathy and Primary IC-MPGN

Unmet needs

2021 GUIDELINES

Unfortunately

No optimal treatment has been established yet for C3G patients



A lot of water has flown under the bridge, and things have significantly changed over the last years...

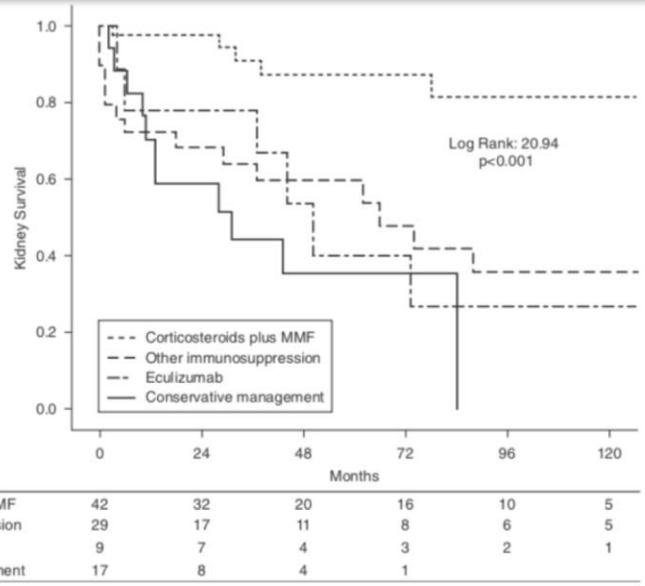
C3 Glomerulopathy and Primary IC-MPGN

MMF

Mycophenolate Mofetil in C3 Glomerulopathy and Pathogenic Drivers of the Disease

Fernando Caravaca-Fontán,[1,2] Montserrat M. Díaz-Encarnación,[3] Laura Lucientes,[4] Teresa Cavero,[5] Virginia Cabello,[6] Gema Ariceta,[7] Luis F. Quintana,[8] Helena Marco,[9] Xoana Barros,[10] Natalia Ramos,[11] Nuria Rodríguez-Mendiola,[12] Sonia Cruz,[13] Gema Fernández-Juárez,[14] Adela Rodríguez,[15] Ana Pérez de José,[16] Cristina Rabasco,[17] Raquel Rodado,[18] Loreto Fernández,[19] Vanessa Pérez Gómez,[20] Ana I. Ávila,[21] Luis Bravo,[22] Javier Lumbreras,[23] Natalia Allende,[24] Maria Dolores Sanchez de la Nieta,[25] Eva Rodríguez,[26] Teresa Olea,[27] Marta Melgosa,[28] Ana Huerta,[29] Rosa Miquel,[30] Carmen Mon,[31] Gloria Fraga,[32] Alberto de Lorenzo,[33] Juliana Draibe,[34] Marta Cano-Megías,[35] Fayna González,[36] Amir Shabaka,[37] Maria Esperanza López-Rubio,[38] María Ángeles Fenollosa,[39] Luis Martín-Penagos,[40] Iara Da Silva,[3] Juana Alonso Titos,[41] Santiago Rodríguez de Córdoba,[42] Elena Goicoechea de Jorge,[3,42] and Manuel Praga,[1,2] on behalf of the Spanish Group for the Study of Glomerular Diseases GLOSEN

CJASN Clinical Journal of American Society of Nephrology



Patients at risk						
Corticosteroids plus MMF	42	32	20	16	10	5
Other immunosuppression	29	17	11	8	6	5
Eculizumab	9	7	4	3	2	1
Conservative management	17	8	4	1		

	Remission (either complete or partial) N (%)	Complete remission N (%)	Partial remission N (%)	No response N (%)	Kidney failure N (%)
Caravaca-Fontán et al (N=42)	33 (78)	15 (36)	18 (43)	9 (27)	6 (14)
Khandelwal 2021 (N=40)	11 (27)	—	—	29 (72)	—
Avasare 2018 (N=30)	20 (66)	10 (33)	10 (33)	10 (33)	3 (10)
Caliskan 2017 (N=27)	16 (59)	11 (41)	5 (19)	11 (41)	7 (26)
Ravindran 2018 (N=24)	3 (12)	1(4)	2 (8)	15 (62)	3 (12)
Rabasco 2015 (N=22)	19 (86)	6 (32)	13 (68)	3 (13)	0 (0)
Bharati 2019 (N=17)	11 (64)	4 (23)	7 (41)	6 (35)	3 (17)
Total (N=202)	113 (55)	47 (29)*	55 (34)*	83 (41)	22 (13)

* Excluding Khandelwal series

Rabasco C et al. Kidney Int. 2015; 88(5): 1153–60.
Avasare RS et al. CJASN. 2018; 13(3): 406–13.
Caravaca Fontan F et al. CJASN 2020; 15: 1287–1298.
Bharati J. Clinical Kidney Journal, 2019; 12: 483–487
Caliskan Am J Nephrol 2017;46:96-107
Khandelwal Pediatric Nephrology (2021) 36:591–600
Ravindran 2018 Mayo Clin Proc. 2018;93(8):991-1008

C3 Glomerulopathy and Primary IC-MPGN

Eculizumab

Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis

CJASN Clinical Journal of American Society of Nephrology

Andrew S. Bomback, Richard J. Smith,† Gaetano R. Barile,‡ Yuzhou Zhang,† Eliot C. Heher,§ Leal Herlitz,‖ M. Barry Stokes,‖ Glen S. Markowitz,‖ Vivette D. D'Agati,‖ Pietro A. Canetta,* Jai Radhakrishnan,* and Gerald B. Appel**

Pathology after Eculizumab in Dense Deposit Disease and C3 GN

JASN

Leal C. Herlitz,* Andrew S. Bomback,† Glen S. Markowitz,* M. Barry Stokes,* R. Neal Smith,‡ Robert B. Colvin,‡ Gerald B. Appel,† and Vivette D. D'Agati*

Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerulopathy

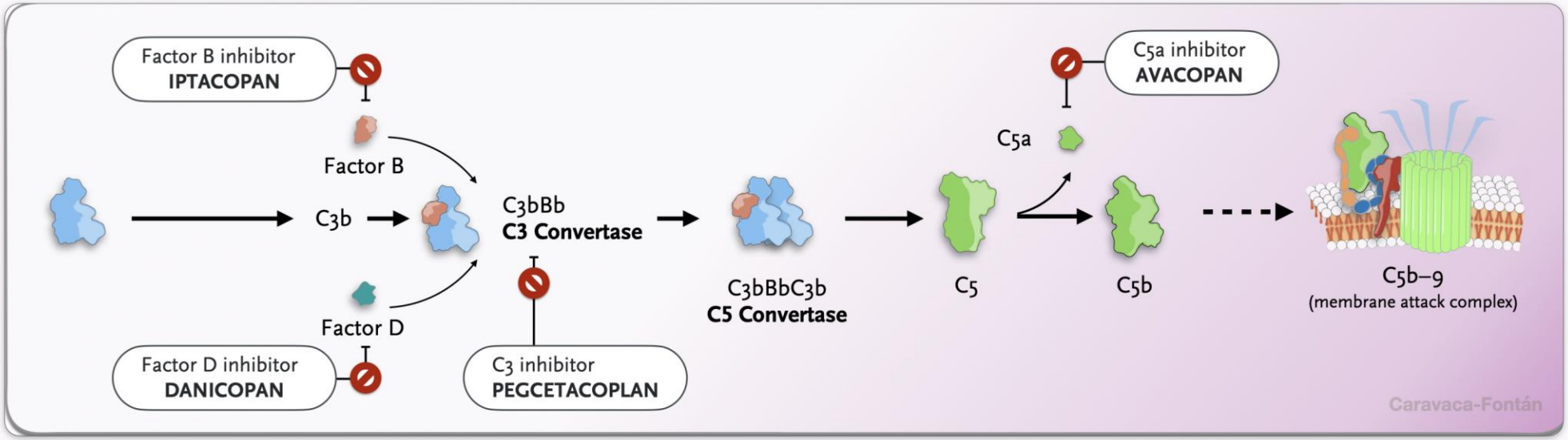
AJKD American Journal of Kidney Diseases

Moglie Le Quintrec, Anne-Laure Lapeyraque, Arnaud Lionet, Anne-Laure Sellier-Leclerc, Yahsou Delmas, Véronique Baudouin, Eric Daugas, Stéphane Decramer, Leila Tricot, Mathilde Cailliez, Philippe Dubot, Aude Servais, Catherine Mourey-Epron, Franck Pourcine, Chantal Loirat, Véronique Frémeaux-Bacchi, and Fadi Fakhouri

- ***26 patients*** *(13 children/adolescents)*
- ***Onset of treatment:*** *42% CKD, 27% rapidly progressive disease, 12% dialysis*
- ***Duration of eculizumab:*** *14 months*
- ***Response: 23% Global clinical response***
  23% Partial clinical response
  54% No response
- ***Conclusions:*** *Eculizumab appears to be a potential treatment for patients with crescentic rapidly progressive C3G. Its benefit in patients with non-rapidly progressing forms seems to be limited.*

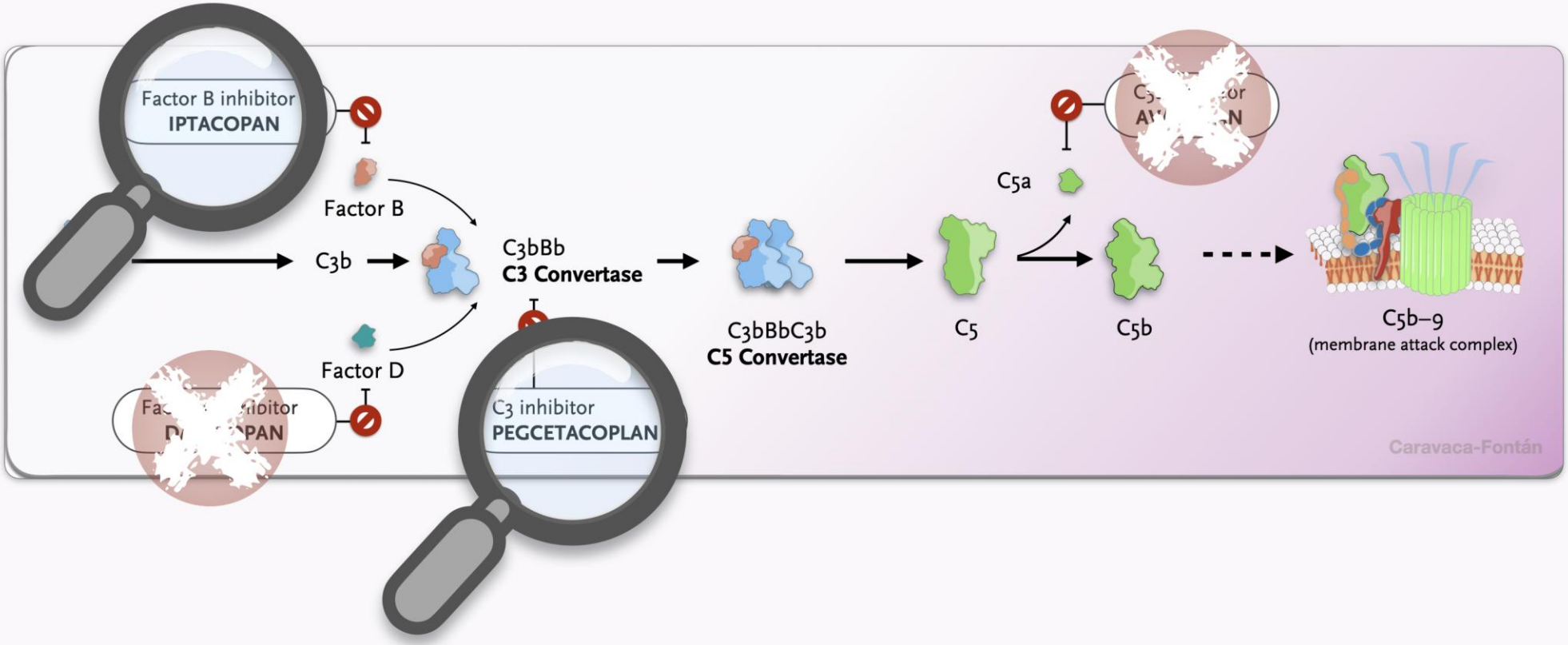
C3 Glomerulopathy and Primary IC-MPGN

Emerging therapies



C3 Glomerulopathy and Primary IC-MPGN

Emerging therapies

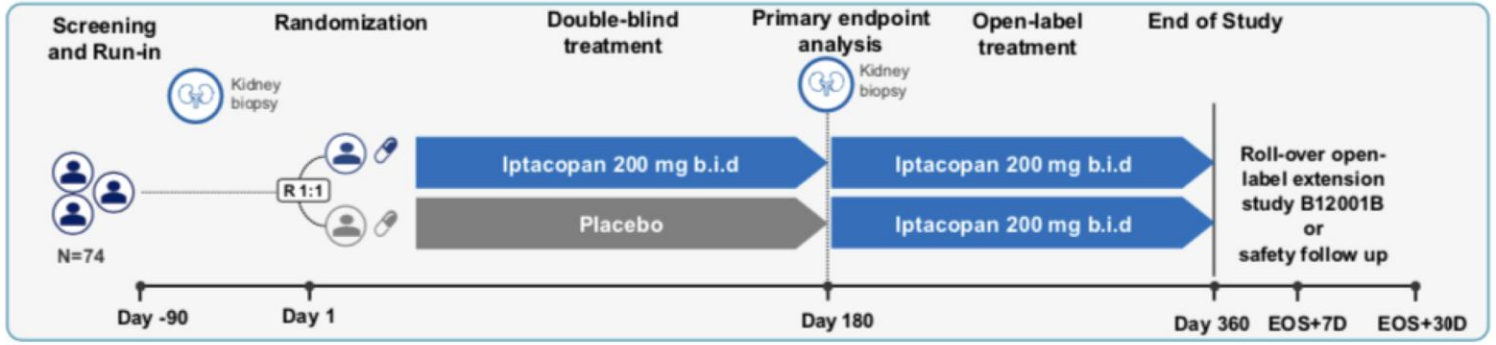


C3 Glomerulopathy and Primary IC-MPGN

Iptacopan

Oral iptacopan therapy in patients with C3 glomerulopathy: a randomised, double-blind, parallel group, multicentre, placebo-controlled, phase 3 study

David Kavanagh, Andrew S Bomback*, Marina Vivarelli, Carla M Nester, Giuseppe Remuzzi, Ming-Hui Zhao, Edwin K S Wong, Yaqin Wang, Induja Krishnan, Imelda Schuhmann, Angelo J Trapani, Nicholas J A Webb, Matthias Meier, Rubeen K Israni, Richard J H Smith, on behalf of APPEAR-C3G investigators†*



Open-label period	
Primary objective	• To evaluate the effect of iptacopan on proteinuria at 12 months
Key secondary objectives	• To evaluate the effect at 12 months of iptacopan on a composite renal endpoint • To evaluate the safety and tolerability of iptacopan over 12-month treatment period

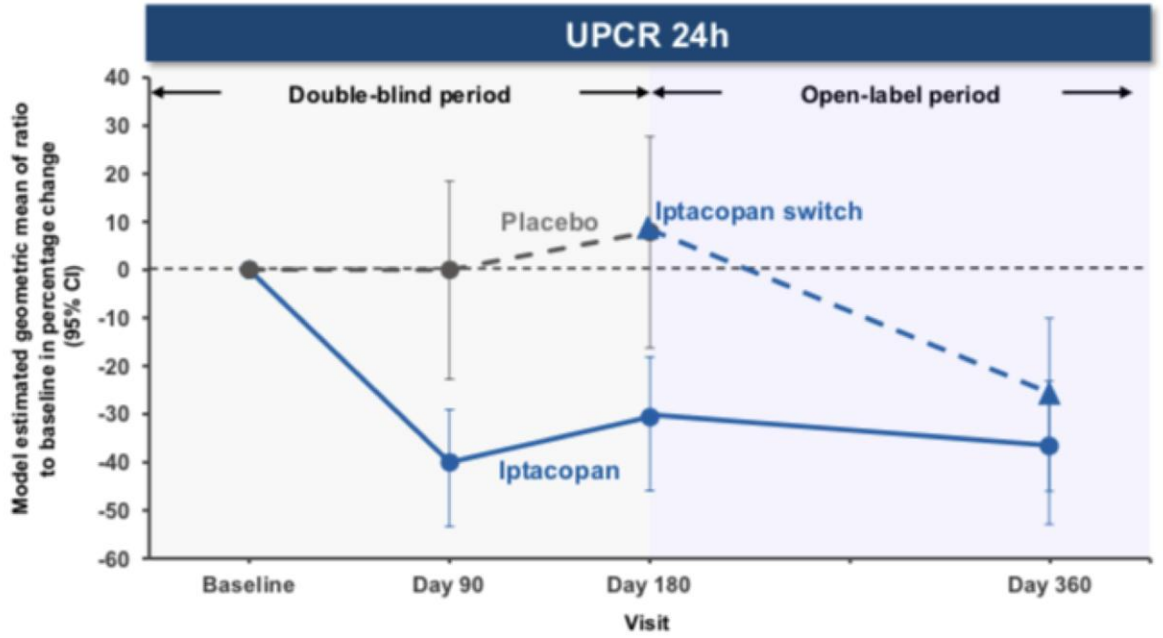
C3 Glomerulopathy and Primary IC-MPGN

Iptacopan

		Iptacopan (N=38)	Placebo (N=36)
Baseline UPCR 24h (g/g) – Geo-mean (95%CI)		**3.33** (2.79, 3.97)	**2.58** (2.18, 3.05)
Baseline total urinary protein (24h) – n (%)	**≥3 g/day**	27 (71.1%)	21 (58.3%)
Baseline UPCR (24h) – n (%)	**≥3 g/g**	21 (55.3%)	11 (30.6%)
Baseline eGFR (mL/min/1.73m²) – Mean (SD)		**89.3** (35.20)	**99.2** (26.88)
Baseline eGFR – n (%)	**<90 mL/min/1.73m²**	19 (50.0%)	12 (33.3%)
Baseline eGFR – n (%)	**<60 mL/min/1.73m²**	10 (26.3%)	4 (11.1%)
Hypertension – n (%)		23 (60.5%)	18 (50.0%)
Age at C3G diagnosis – n (%)	**<18 years**	15 (39.5%)	6 (16.7%)
Time since first C3G diagnosis – n (%)	**<2 years**	15 (39.5%)	15 (41.7%)
Baseline RASi use – n (%)		37 (97.4%)	36 (100%)
Corticosteroid and/or mycophenolic acid at randomization	**Yes**	16 (42.1%)	17 (47.2%)
C3G subtype at diagnosis – n (%)	**C3GN**	26 (68.4%)	32 (88.9%)
	DDD	9 (23.7%)	1 (2.8%)
	Mixed C3GN/DDD	2 (5.3%)	2 (5.6%)

C3 Glomerulopathy and Primary IC-MPGN

Iptacopan



Proteinuria reduction between iptacopan and placebo at Month 6
35.1%
(1-sided p-value: 0.0014)

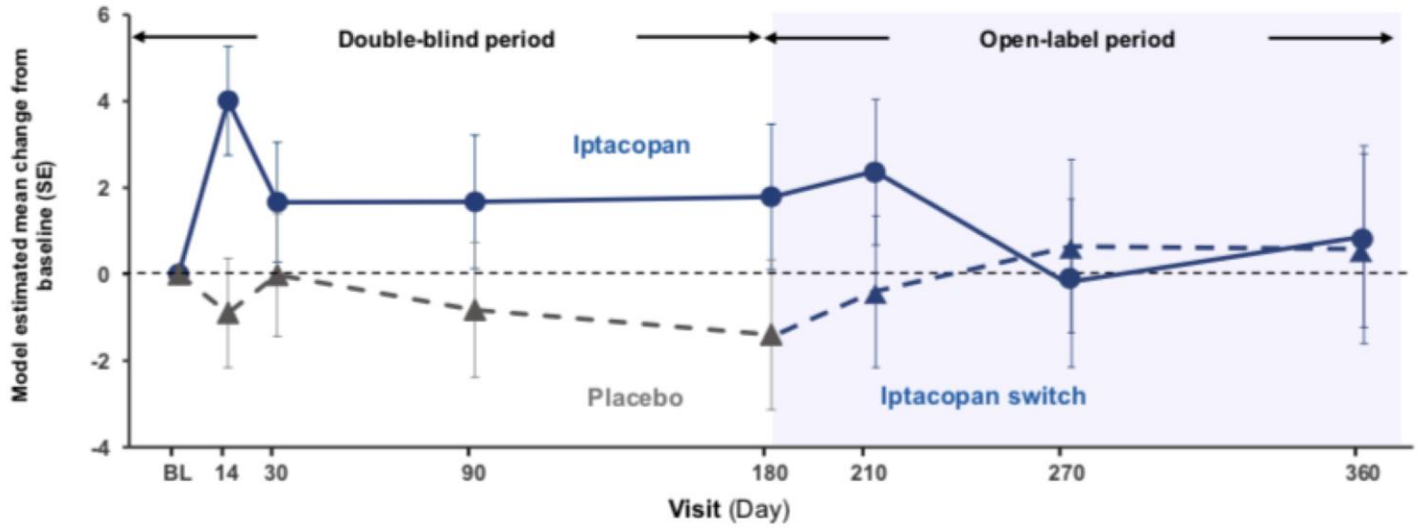
Proteinuria reduction following switch from placebo to iptacopan
(-31% from Month 6 to 12)*

Sustained proteinuria reduction to 12 months in iptacopan arm
(-37% from baseline)

C3 Glomerulopathy and Primary IC-MPGN

Iptacopan

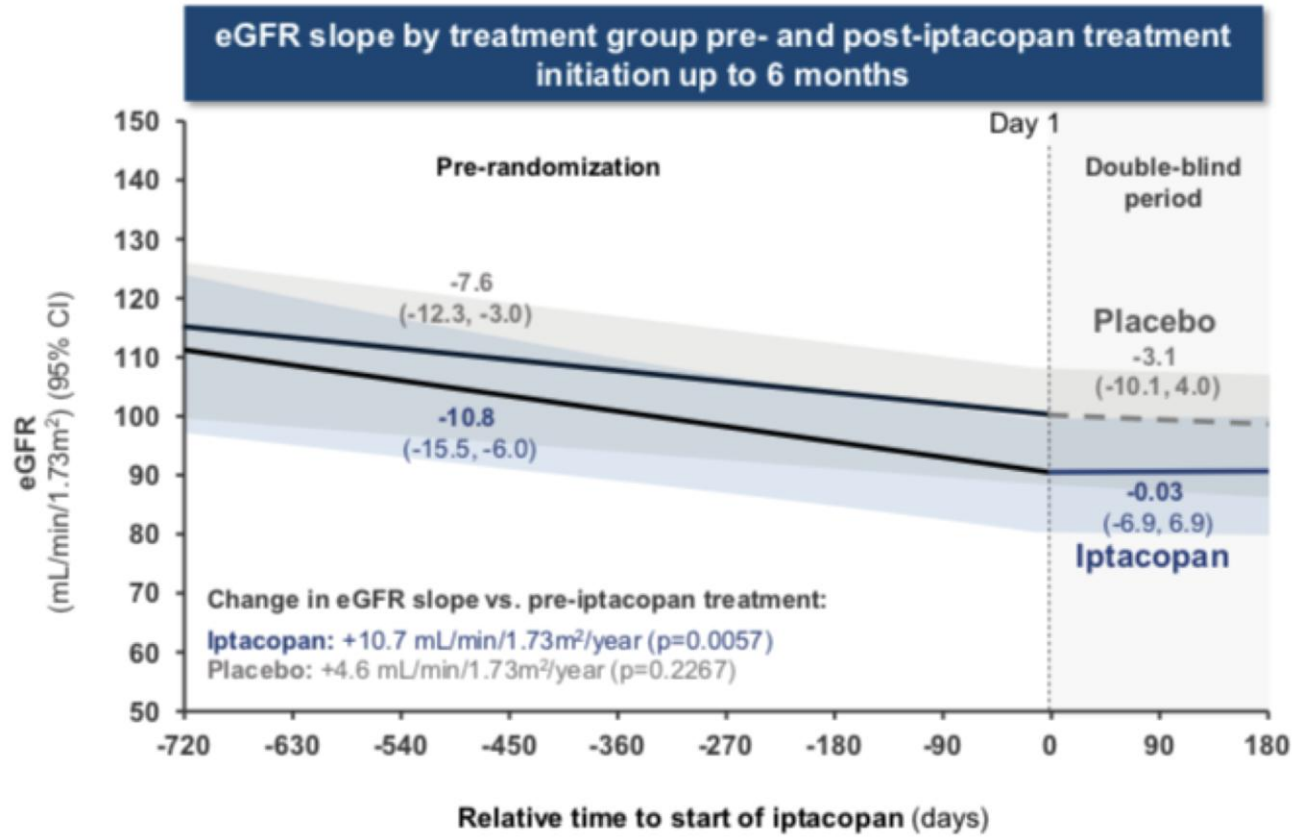
eGFR Change from Baseline to Month 12 (adjusted for baseline UPCR imbalance [Post-hoc analysis])



Iptacopan stabilized eGFR in placebo arm after switching to open-label Iptacopan

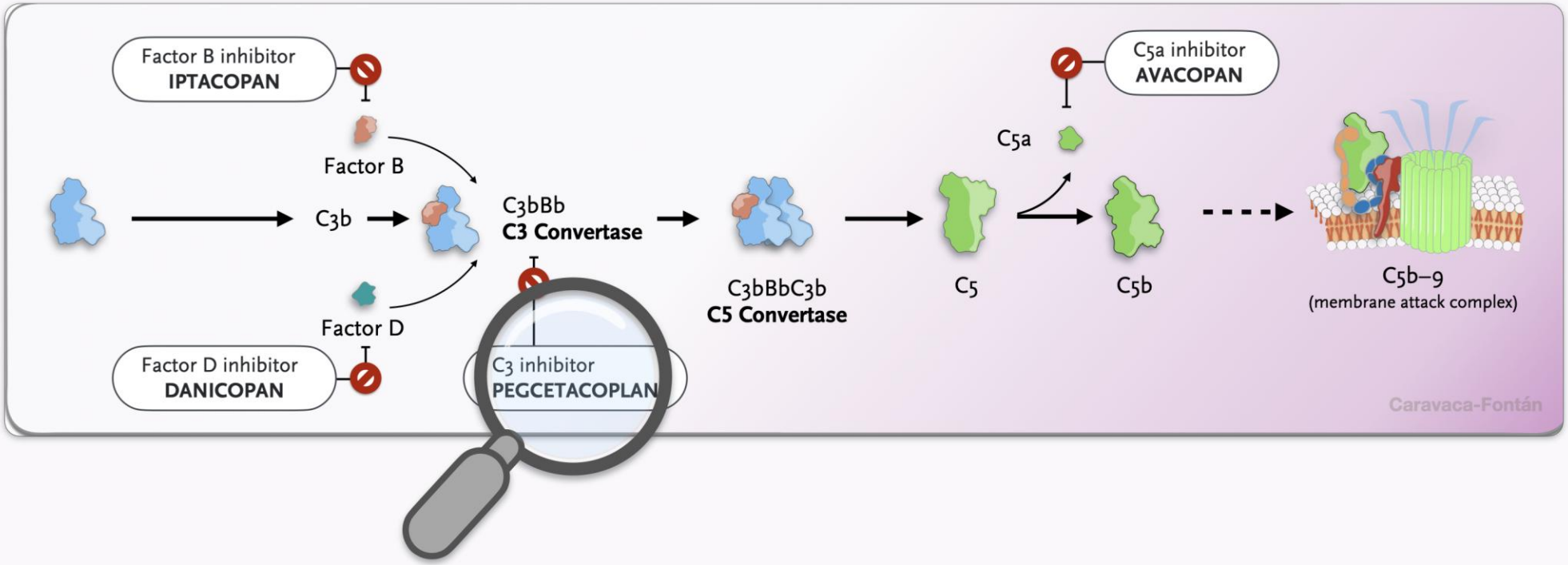
C3 Glomerulopathy and Primary IC-MPGN

Iptacopan



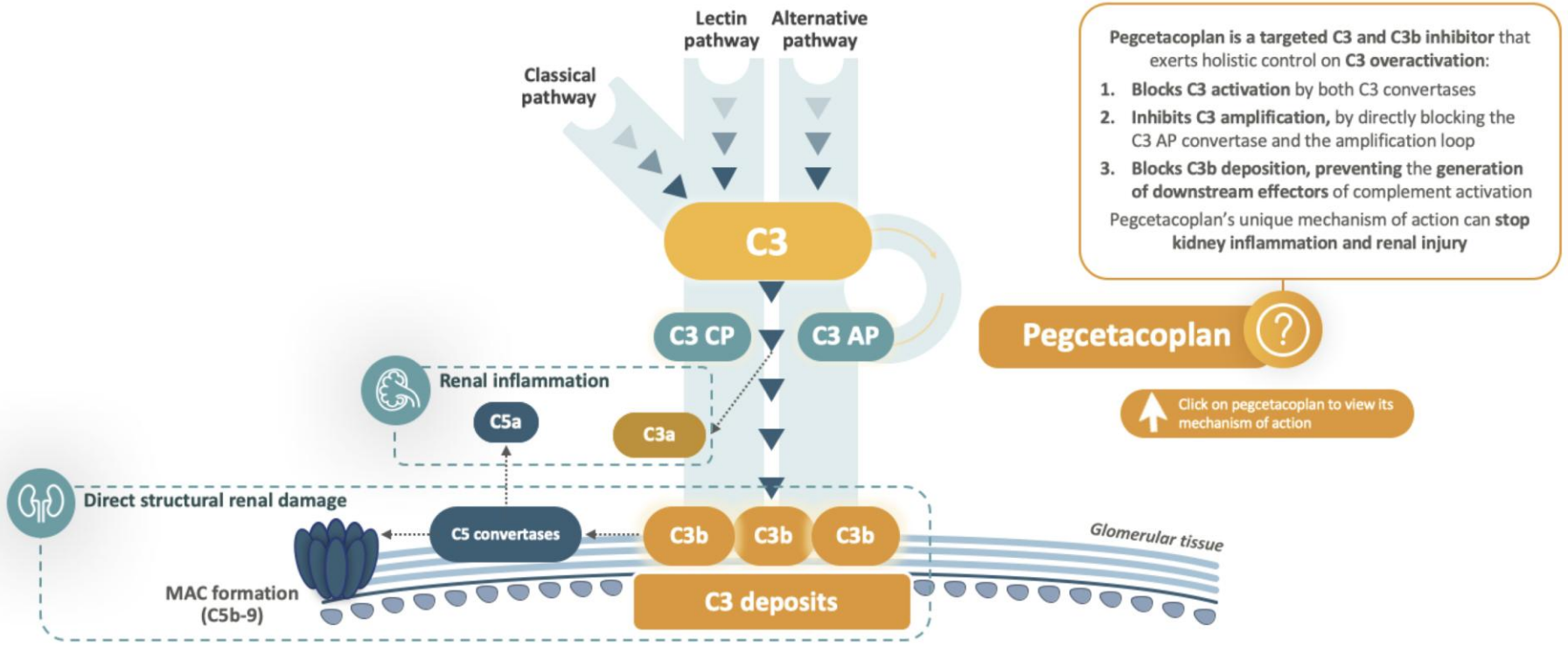
C3 Glomerulopathy and Primary IC-MPGN

Emerging therapies



C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan



C3 Glomerulopathy and Primary IC-MPGN

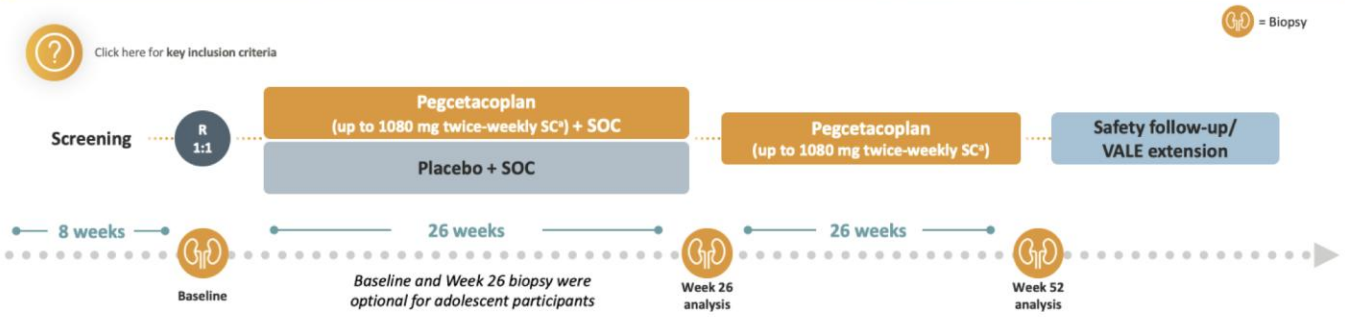
Pegcetacoplan

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Pegcetacoplan in C3 Glomerulopathy and Immune-Complex MPGN

F. Fakhouri,[1,2] A.S. Bomback,[3] G. Ariceta,[4] Y. Delmas,[5] B.P. Dixon,[6] D.P. Gale,[7] L.A. Greenbaum,[8,9] S.H. Han,[10] N. Isbel,[11,12] M. Le Quintrec,[13] C. Licht,[14,15] A. Mastrangelo,[16] M. Mizuno,[17] M.I. Neves de Holanda,[18] M.C. Pickering,[19] G. Remuzzi,[20] N. Van De Kar,[21] M. Vivarelli,[22] P.D. Walker,[23] D. Wallace,[24] D. Zecher,[25] C. Francois,[26] P. Deschatelets,[26] L. Li,[26] Z. Wang,[26] L. Abad-Franch,[27] N. Kinnman,[27] L. López-Lázaro,[27] J. Szamosi,[27] and C.M. Nester,[28] for the VALIANT Trial Investigators Group*

VALIANT Phase 3 study design: ≥12 years old, native/recurrent C3G or primary IC-MPGN[1,2]



C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

VALIANT baseline demographics: broad patient population

Characteristic[†]	Pegcetacoplan (N=63)	Placebo (N=61)
Age	28.2 (17.1)	23.6 (14.3)
Adolescents (12–17 years)/adults (≥18 years), n (%)	28 (44.4)/35 (55.6)	**27 (44.3)**/34 (55.7)
Age of adolescents/adults, mean (SD), years	14.6 (1.7)/39.1 (15.9)	14.8 (1.7)/30.6 (15.9)
Sex, female, n (%)	37 (58.7)	33 (54.1)
Race, white, n (%)	45 (71.4)	46 (75.4)
Baseline 24 hr uPCR, mean (SD), g/g	3.95 (2.89)	3.29 (2.36)
Baseline triplicate first-morning spot uPCR, mean (SD), g/g	3.12 (2.41)	2.54 (2.01)
Baseline eGFR, mean (SD), mL/min/1.73 m²	78.5 (34.1)	87.2 (37.2)
Underlying disease based on screening biopsy, n (%)		
C3G	51 (81.0)	**45 (73.8)**
C3GN	45 (71.4)	41 (67.2)
DDD	4 (6.3)	4 (6.6)
Undetermined	2 (3.2)	0 (0.0)
Primary IC-MPGN	12 (19.0)	**16 (26.2)**
Time since diagnosis, mean (SD), years	3.6 (3.5)	3.8 (3.6)
Post-transplant recurrent disease, n (%)	5 (7.9)	**4 (6.6)**

[†]Intention-to-treat population (all randomised patients).
C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; hr, hour; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; SD, standard deviation; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

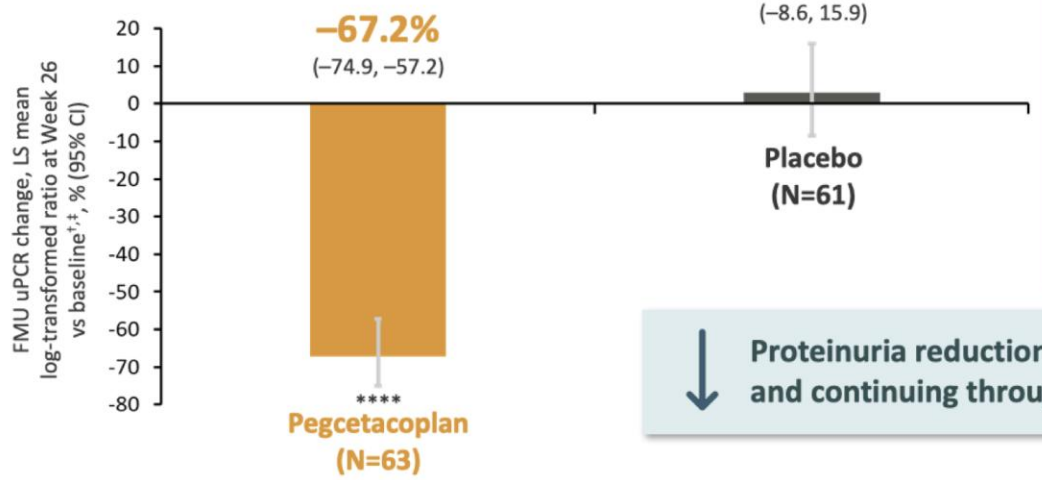
NP-37604

C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

Highly statistically and clinically significant proteinuria reduction of 68.1% with pegcetacoplan vs placebo

Change in proteinuria (Week 26 vs baseline)[†,‡]



Primary endpoint

Relative reduction[‡] (95% CI) in pegcetacoplan vs placebo

68.1%

(57.3, 76.2)

p<0.0001

↓ **Proteinuria reduction observed as early as Week 4 and continuing through Week 26**

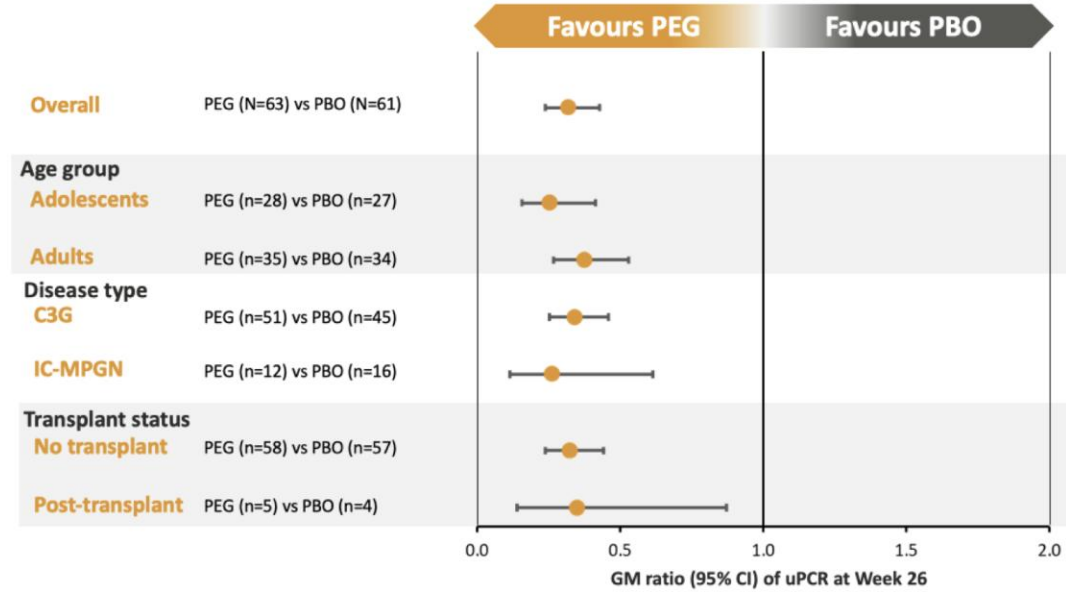
****p≤0.0001. Intention-to-treat population (all randomised patients).
[†]Using an equal-weighted average from FMU over Weeks 24, 25 and 26. [‡]Percentages calculated by converting the ratio of geometric means to percentages.
CI, confidence interval; FMU, first-morning spot urine; LS, least squares; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

NP-37604

C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

Consistent, clinically meaningful proteinuria reductions with pegcetacoplan vs placebo were observed across broad patient subgroups



		Relative reduction in proteinuria at Week 26† PEG vs PBO‡
Overall	PEG (N=63) vs PBO (N=61)	68.1% (p<0.0001)
Age group		
Adolescents	PEG (n=28) vs PBO (n=27)	74.5% (p<0.0001)
Adults	PEG (n=35) vs PBO (n=34)	62.5% (p<0.0001)
Disease type		
C3G	PEG (n=51) vs PBO (n=45)	65.8% (p<0.0001)
IC-MPGN	PEG (n=12) vs PBO (n=16)	73.7% (p=0.002)
Transplant status		
No transplant	PEG (n=58) vs PBO (n=57)	67.5% (p<0.0001)
Post-transplant	PEG (n=5) vs PBO (n=4)	64.9% (p=0.024)

Intention-to-treat population (all randomised patients).
†Using an equal-weighted average over Weeks 24, 25, and 26 compared with baseline. ‡Percentages calculated by converting the ratio of geometric means to percentages.
C3G, complement 3 glomerulopathy; CI, confidence interval; GM, geometric mean; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; PBO, placebo; PEG, pegcetacoplan; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

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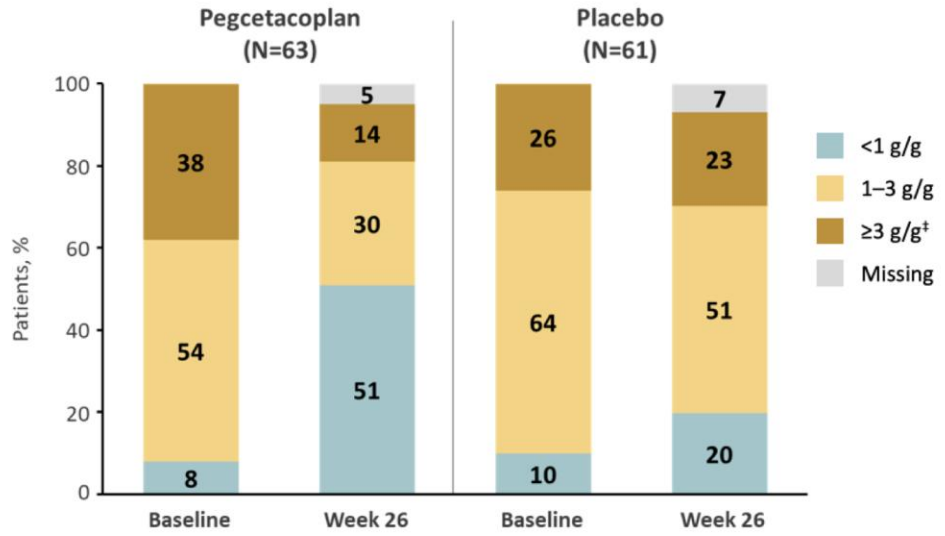
C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

Substantial improvement in the percentage of patients with proteinuria <1 g/g and decrease in percentage in nephrotic range (≥3 g/g) following pegcetacoplan treatment

Proteinuria shift analysis (Week 26 vs baseline)†



Post-hoc analysis

Proportion of pegcetacoplan-treated patients with

<1 g/g proteinuria

after 26 weeks

50.8%

†Based on FMU uPCR. ‡Nephrotic range
FMU, first-morning spot urine; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

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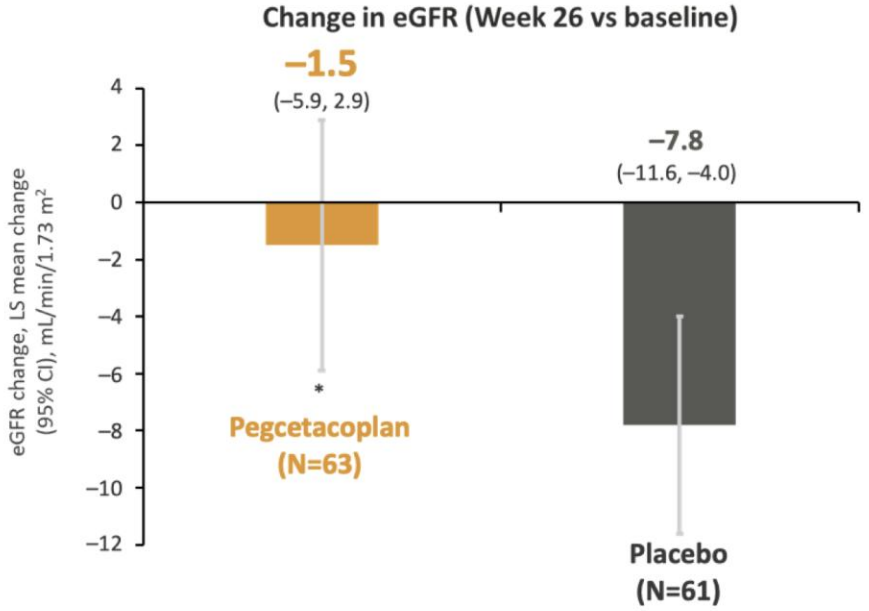
C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

Pegcetacoplan significantly stabilised eGFR compared with placebo



Key secondary endpoint

Difference in pegcetacoplan vs placebo

+6.3 mL/min/1.73 m²

P=0.03 nominal†

*p≤0.05. Intention-to-treat population (all randomised patients). †Statistical testing stopped after first endpoint to not reach significance between treatment arms (i.e., change in activity score of C3G histologic index score at Week 26 vs baseline).
CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least squares.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

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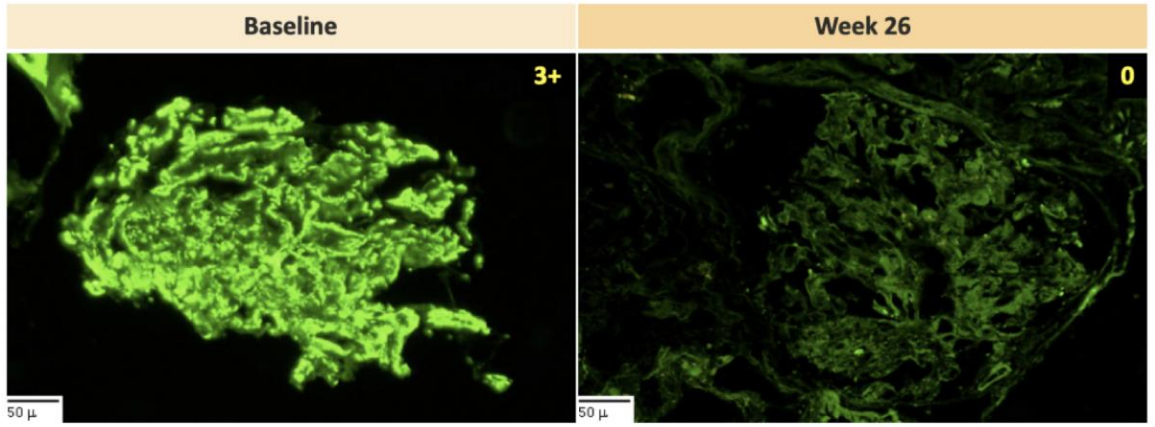
C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

Pegcetacoplan treatment stopped C3 deposition as seen by C3 staining in renal biopsy

Renal biopsies from a pegcetacoplan-treated C3G native kidney patient:



71.4% (25/35) of pegcetacoplan-treated patients achieved 0 intensity staining

Key secondary endpoint	
Proportion with reduced C3c renal biopsy staining†	
Pegcetacoplan	74.3% (26/35)
Placebo	11.8 (4/34)

27x higher odds of achieving ≥2 OOM reduction
(6.5, 115.9); nominal‡
p<0.0001

†Difference defined as ≥2 OOM at Week 26 vs baseline; in all adults. Baseline renal biopsies were not required for adolescent participants.
‡Statistical testing stopped after first endpoint to not reach significance between treatment arms (i.e., change in activity score of C3G histological index score at Week 26 vs baseline).
C3c, complement 3c; C3G, complement 3 glomerulopathy; OOM, orders of magnitude.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

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C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

Pegcetacoplan was well tolerated:
TEAE frequency and severity were similar between treatment arms

Patients, n (%)	Pegcetacoplan (N=63)	Placebo (N=61)
TEAEs	53 (84.1)	57 (93.4)
Treatment-related TEAEs	25 (39.7)	26 (42.6)
Severe TEAEs	3 (4.8)	4 (6.6)
Serious TEAEs	6 (9.5)	6 (9.8)
Serious infections		
COVID-19 pneumonia	1 (1.6)	0 (0.0)
Influenza	1 (1.6)	0 (0.0)
Pneumonia	1 (1.6)	0 (0.0)
Viral infection	0 (0.0)	1 (1.6)
TEAEs leading to treatment discontinuation	1 (1.6)	1 (1.6)
Deaths (COVID-19 pneumonia, unrelated to pegcetacoplan)	1 (1.6)	0 (0.0)

No encapsulated *N. meningitidis*
cases among the four reported serious infections (pegcetacoplan, n=3; placebo, n=1)

Consistent with >2,000 patient-years of pegcetacoplan exposure†

Safety population (all randomised and treated patients). TEAEs defined as any new AE that began, or any preexisting condition that worsened in severity, after the first dose of study drug and ≤56 days beyond the last dose of study drug.
†Includes exposure in clinical trials and post marketing across multiple indications.
AE, adverse event; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent AE.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

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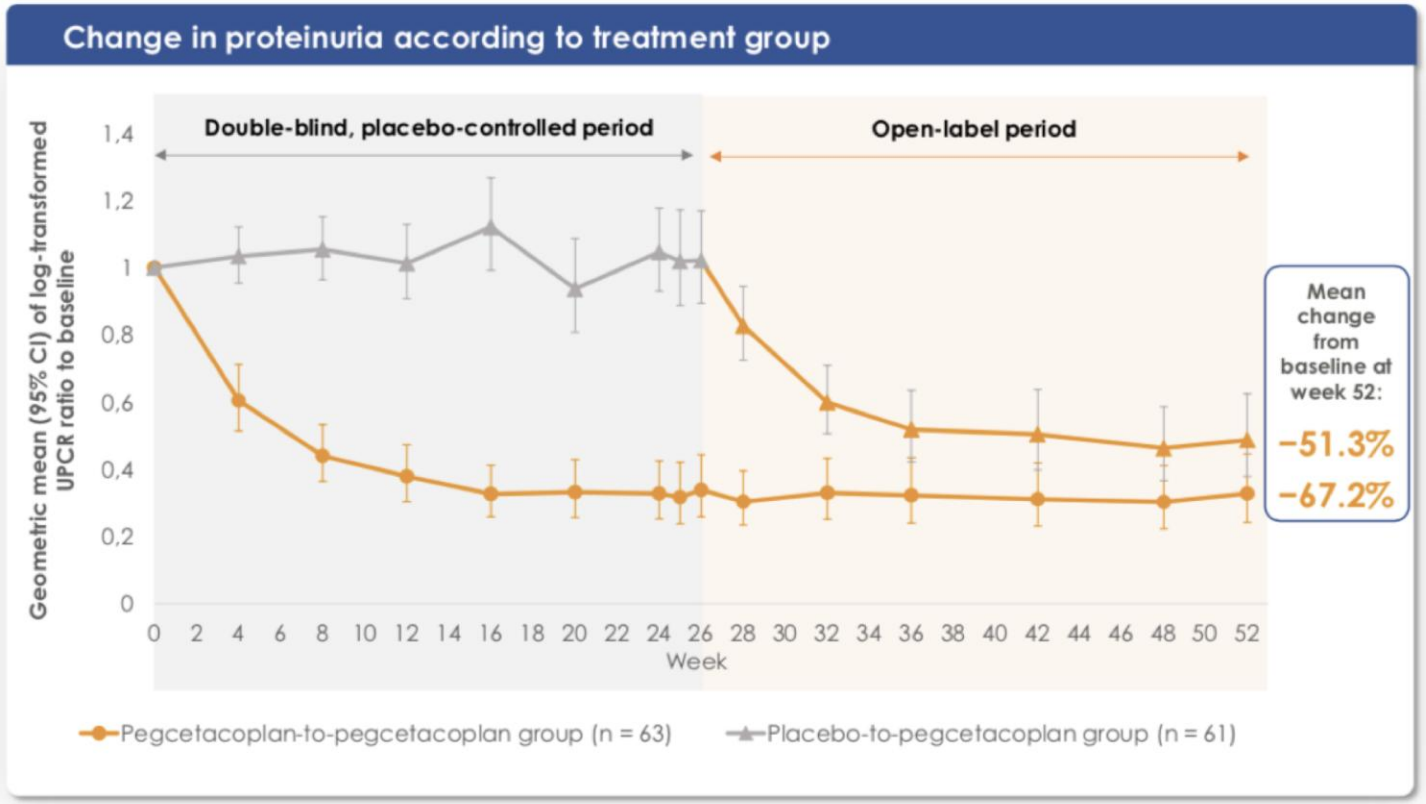
C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

Robust **proteinuria reductions** at week 26 **were maintained** through week 52



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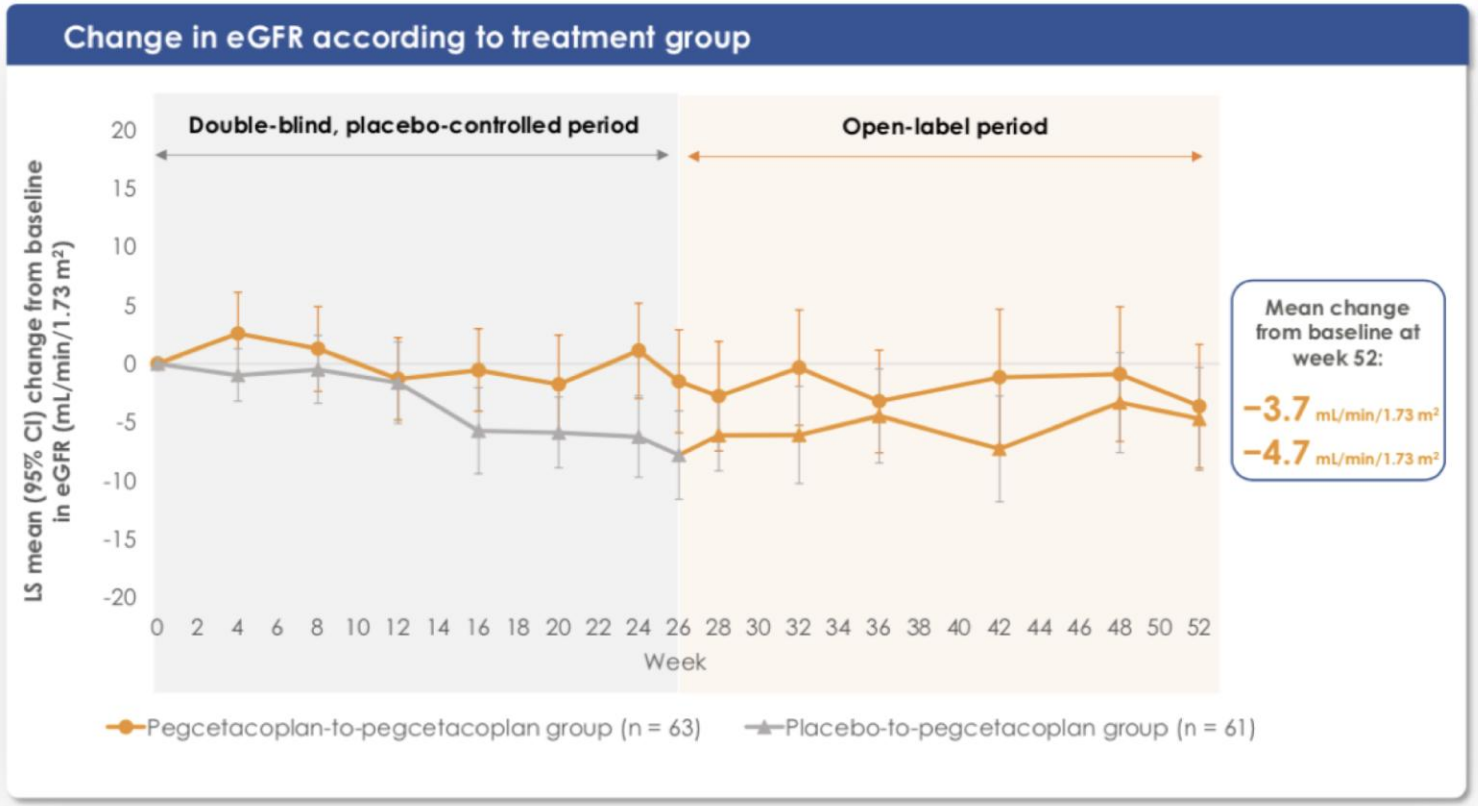
C3 Glomerulopathy and Primary IC-MPGN

Pegcetacoplan

eGFR remained stable for both groups for the duration of the study



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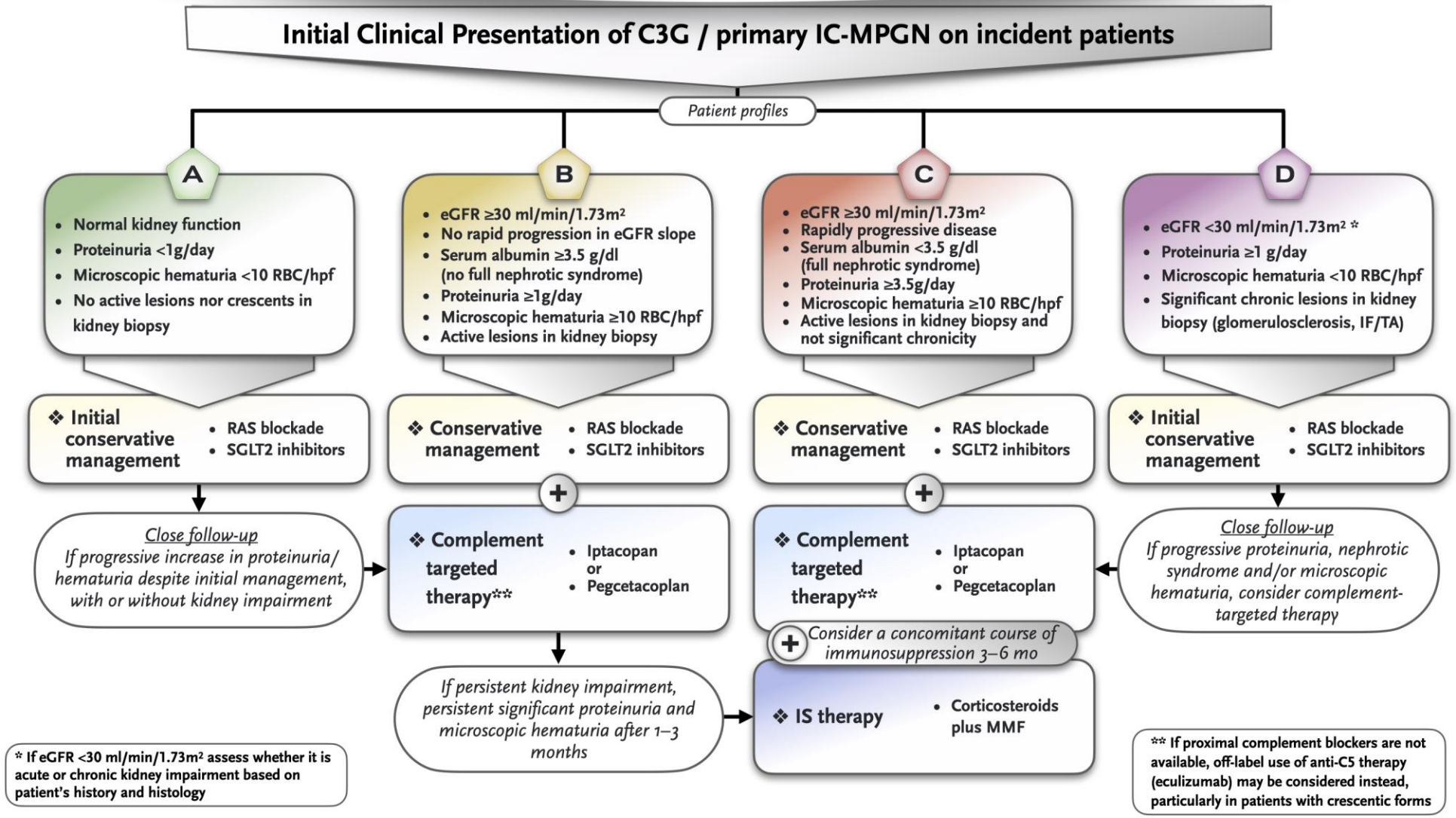
C3 Glomerulopathy and Primary IC-MPGN

Personal view



C3 Glomerulopathy and Primary IC-MPGN

Conclusions

- *Highly heterogeneous disease*
- *Associated with dismal outcomes in a significant number of patients*
- *Promising results with new proximal complement inhibitors (pegcetacoplan and iptacopan)*
- *Significant reductions in proteinuria, stabilization of renal function, histological improvement*
- *Overall favorable safety and tolerability profile*
- *Nevertheless, important knowledge gaps still remain, requiring further studies and clinical trials*

Thank you!

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