



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Important New Trials In Glomerular Disease

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Research Focus: Urate transport

Clinical Focus: Glomerulonephritis,

Electrolyte disorders, Gout,

Consultative Nephrology



Financial Disclosures

Author, peer reviewer – UpToDate, McGraw Hill
Consultant/advisory boards
– Gout: Shanton Pharma
– ANCA-associated vasculitis: Amgen



OBJECTIVES

- Review recent developments/trials in IgAN
- Review the development and downfall of avacopan.
- Review recent developments/trials in lupus nephritis and membranous GN.



IgA Nephropathy Epidemiology Analysis



377,829

7MM Prevalence in 2020



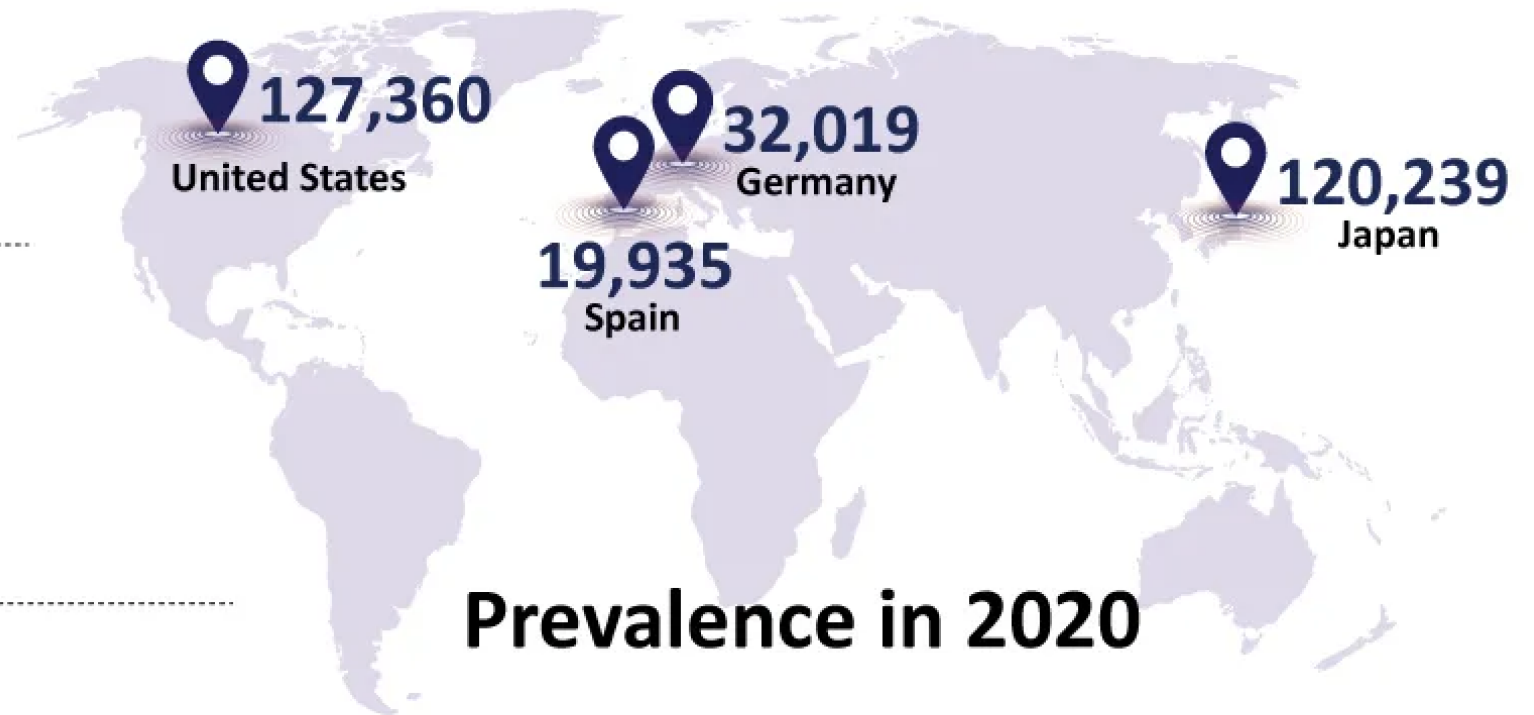
69,191

Prevalence in Males
in the US in 2020



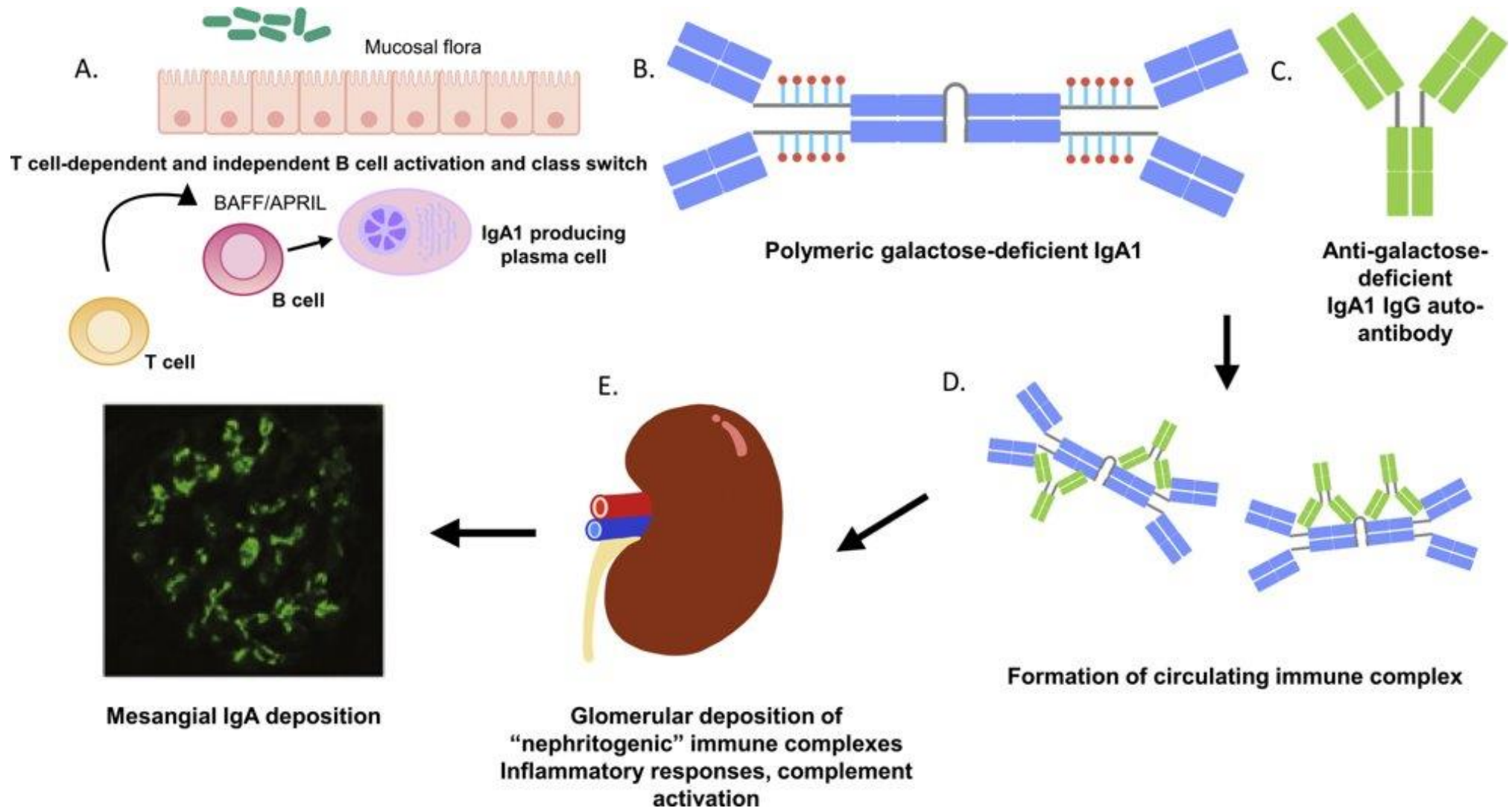
58,169

Prevalence in Females
in the US in 2020

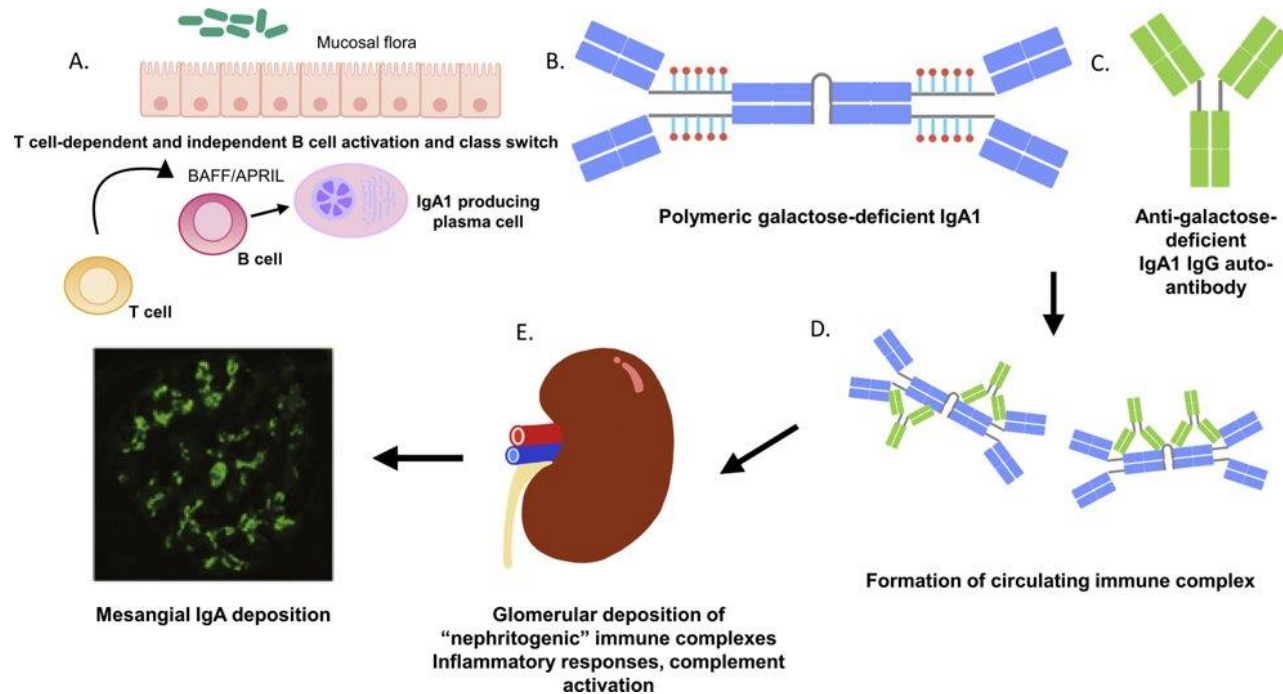


Prevalence in 2020

IgA Nephropathy pathogenesis is complex.

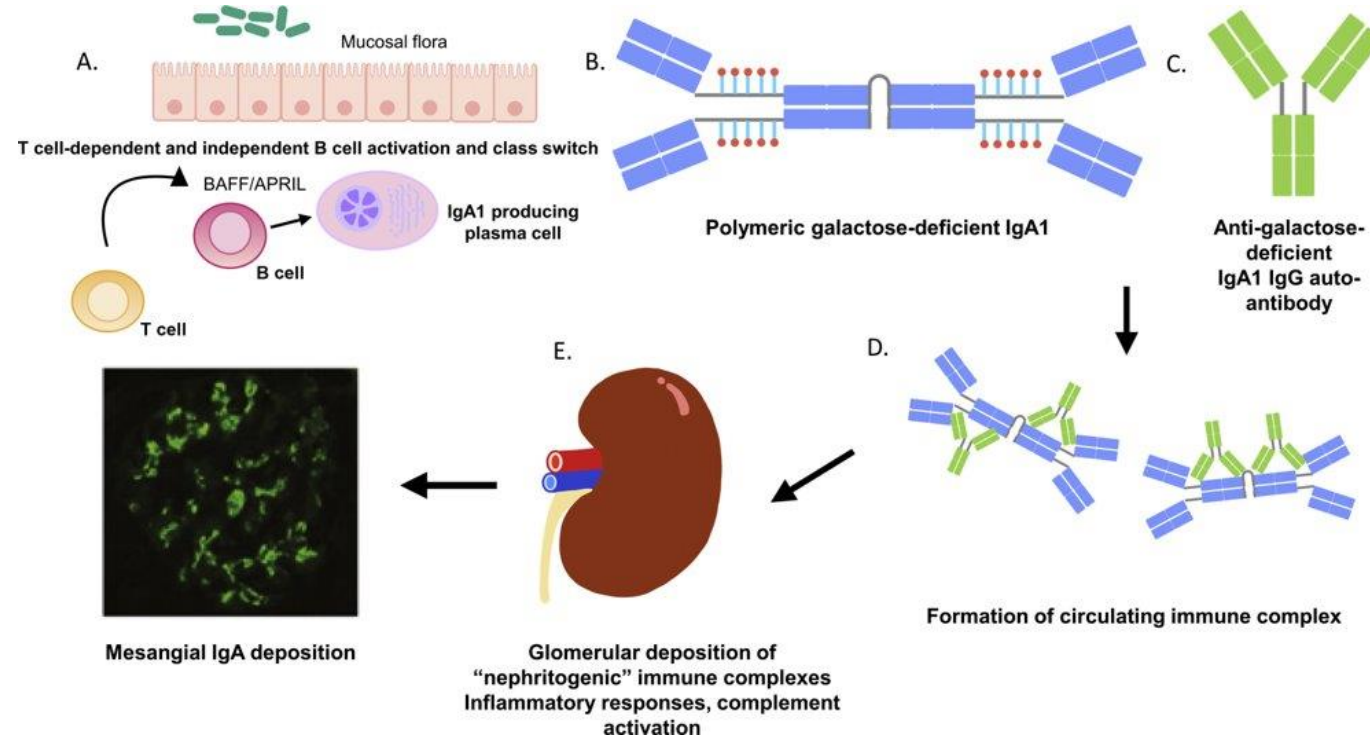


IgA Nephropathy pathogenesis is complex.



1st Hit - Production of poorly glycosylated IgA1 (Gd-IgA1).

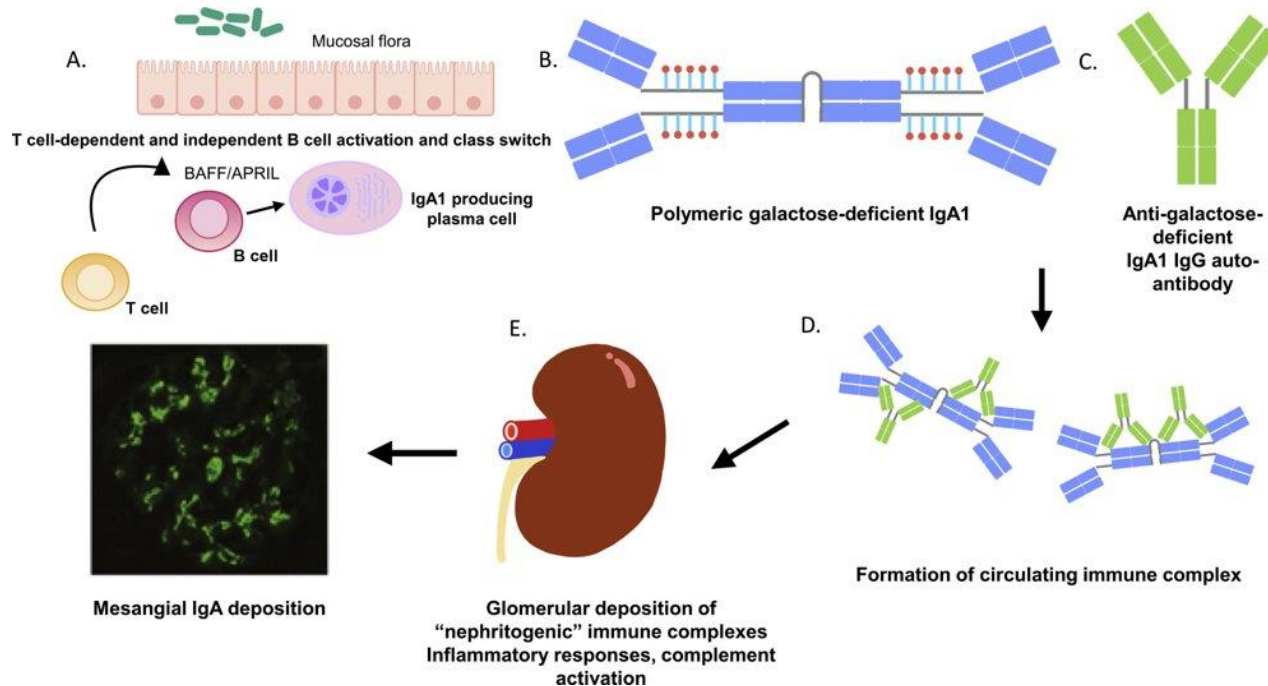
IgA Nephropathy pathogenesis is complex.



1st Hit - Production of poorly glycosylated IgA1 (Gd-IgA1).

2nd Hit - Production of anti-Gd-IgA1 antibodies (IgG or IgA).

IgA Nephropathy pathogenesis is complex.

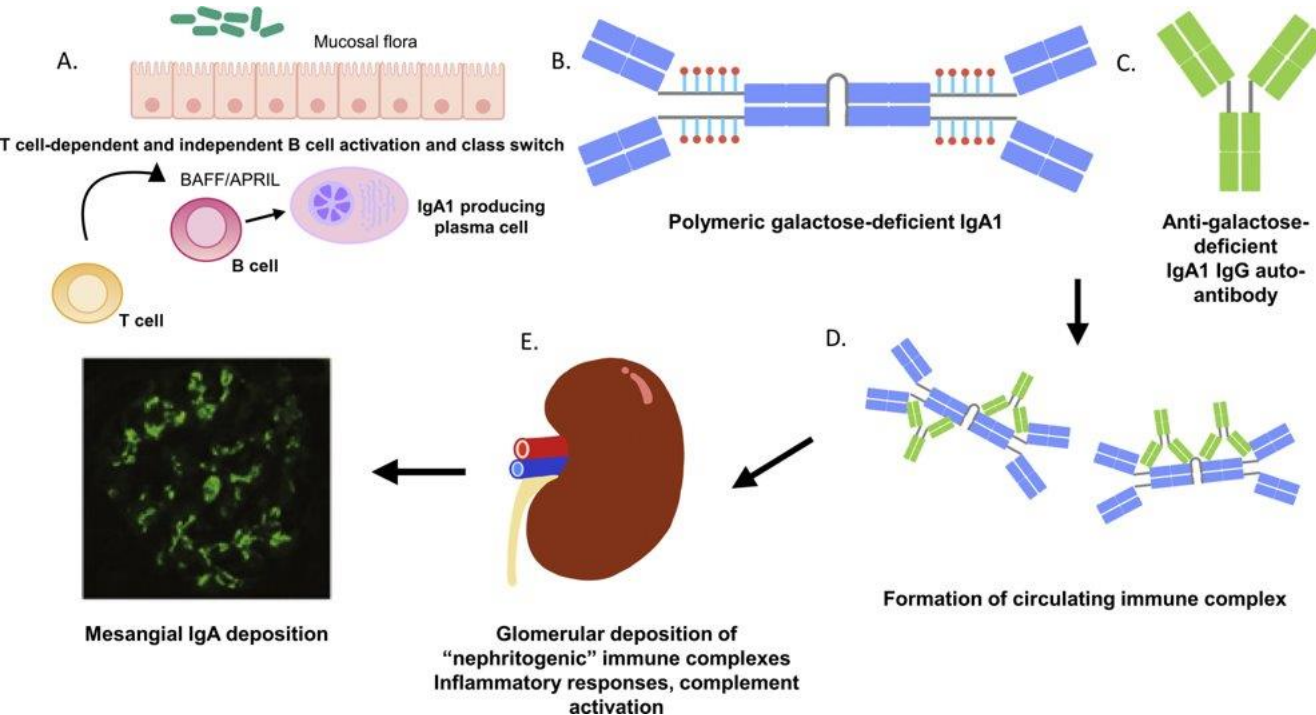


1st Hit - Production of poorly glycosylated IgA1 (Gd-IgA1).

2nd Hit - Production of anti-Gd-IgA1 antibodies (IgG or IgA).

3rd Hit - Formation of circulating immune complexes containing Gd-IgA1.

IgA Nephropathy pathogenesis is complex.



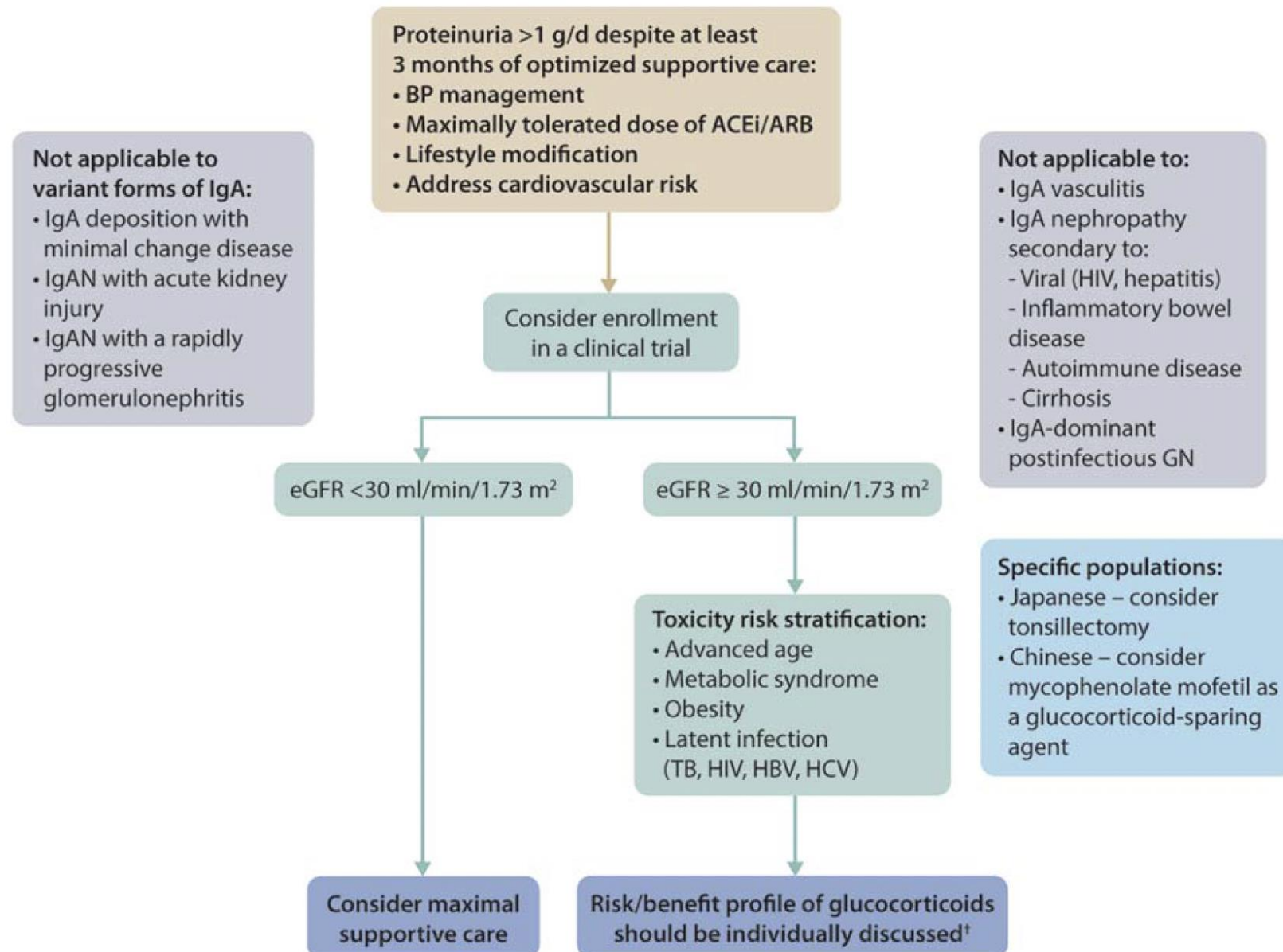
1st Hit - Production of poorly glycosylated IgA1 (Gd-IgA1).

2nd Hit - Production of anti-Gd-IgA1 antibodies (IgG or IgA).

3rd Hit - Formation of circulating immune complexes containing Gd-IgA1.

4th Hit - Immune complex deposition and kidney injury

KDIGO includes consideration of trial enrollment upfront.



Selective Review of IgAN Trials



QUESTION What are the effects of oral glucocorticoids, compared with placebo, in patients with IgA nephropathy and proteinuria of 1 g per day or greater receiving optimal supportive therapy?

CONCLUSION Treatment with oral methylprednisolone significantly reduced the risk of the composite of kidney function decline, kidney failure, or death due to kidney disease in patients with IgA nephropathy, but the incidence of serious adverse events was increased.

POPULATION

305 Men
198 Women



Adults with IgA nephropathy and proteinuria ≥ 1 g per day

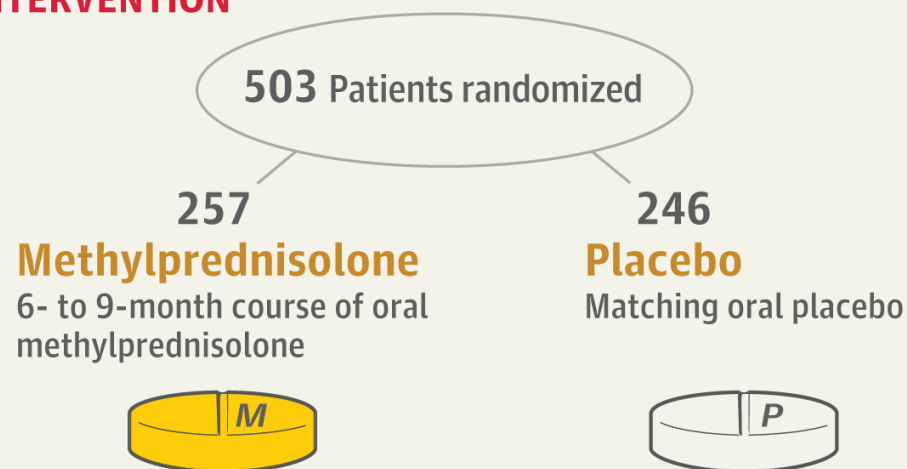
Mean age: 38 years

LOCATIONS

67
Medical centers
worldwide



INTERVENTION



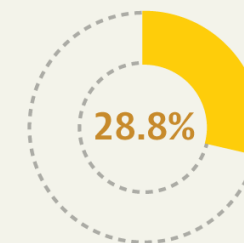
PRIMARY OUTCOME

Composite outcome of the first occurrence of a sustained 40% decrease in estimated glomerular filtration rate, kidney failure, or death due to kidney disease

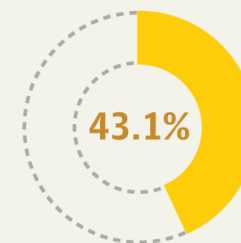
FINDINGS

Patients with composite primary outcome

Methylprednisolone
74 of 257 patients



Placebo
106 of 246 patients



The primary outcome occurred significantly less frequently in the methylprednisolone group:

Hazard ratio, **0.53**

(95% CI, 0.39 to 0.72); $P < .001$

Absolute annual event rate difference, **-4.8%**
(95% CI, -8.0% to -1.6%)

Role of Systemic Glucocorticoids in Reducing IgA and Galactose-Deficient IgA1 Levels in IgA Nephropathy

Jincan Zan,¹ Jingyi Li ¹ Muh Geot Wong ^{2,3,4} Dana Kim ^{2,3} Sufang Shi ¹ Helen Monaghan ² Vlado Perkovic,² Jicheng Lv,¹ and Hong Zhang,¹ for the TESTING study biomarker group*

Key Points

- Systemic glucocorticoids could reduce levels of total IgA and galactose-deficient IgA1 (Gd-IgA1) in IgA nephropathy patients, but the effect diminished after treatment discontinuation.
- The reduction in Gd-IgA1 levels correlates with a decrease in proteinuria in patients treated with glucocorticoids.
- However, the reduction in Gd-IgA1 levels at 6 months during the treatment is not associated with long-term kidney outcomes.

Abstract

CJASN 20: 1564–1570, 2025.

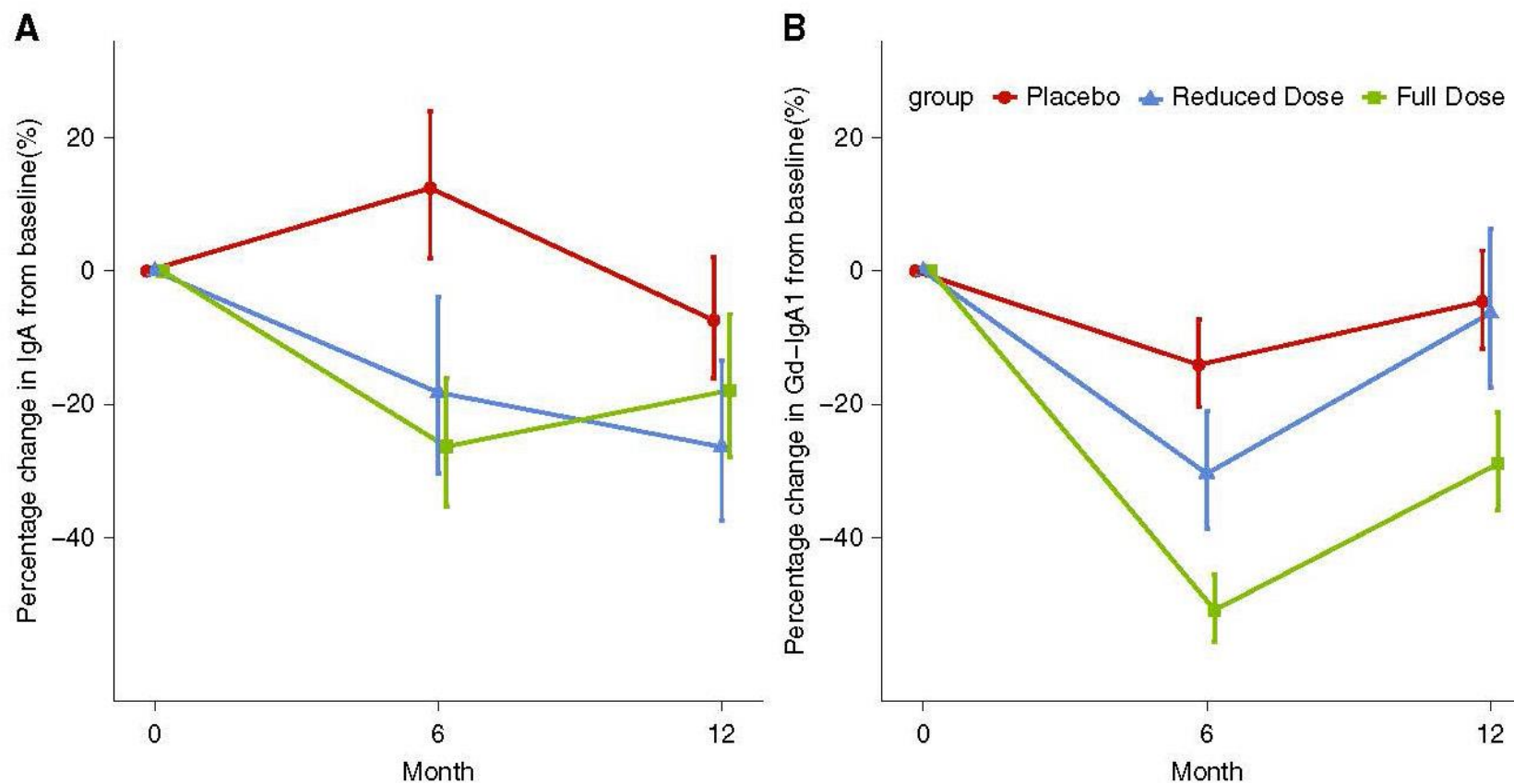


Figure 1. Change in total IgA and Gd-IgA1 from baseline. Percentage changes in (A) total IgA and (B) Gd-IgA1 from baseline at different intervention group. The mean percent change is calculated as $(\text{exponentiated least-squares mean} - 1) \times 100\%$. Bars indicate the 95% CI. CI, confidence interval; Gd-IgA1, galactose-deficient IgA1.

Targeted-release formulation budesonide

- 201 patients with IgAN
- Targeted release budesonide (n = 97).
- Placebo (n = 102).
- Treatment for 9 months.
- All had optimized RAS blockade.
- Median proteinuria 1.26 g/g.
- 58% of patients had proteinuria $\geq 2\text{g/d}$.
- Median eGFR: 55 mL/min/1.73 m²



Targeted-release formulation budesonide

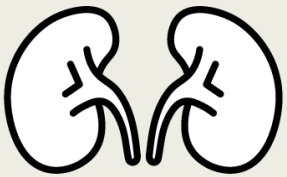
- 201 patients with IgAN
- Targeted release budesonide (n = 97).
- Placebo (n = 102).
- Treatment for 9 months.
- All had optimized RAS blockade.
- Median proteinuria 1.26 g/g.
- 58% of patients had proteinuria ≥ 2 g/d.
- Median eGFR: 55 mL/min/1.73 m²
- At 9 months, UPCR was 27% lower compared with placebo, along with an eGFR preservation of 3.87 mL/min/1.73 m² difference versus placebo.
- TEAEs: 86.6% in Targeted release budesonide vs 73% in placebo. Mostly mild to moderate.
- No severe infections requiring hospitalization.



RCT: Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy

POPULATION

94 Males, 76 Females



Patients with immunoglobulin A (IgA) nephropathy with proteinuria ≥ 0.75 g/d
Mean age, 36.6 y

INTERVENTION

170 Patients randomized



85 Supportive care (SC) group

Blockade of renin-angiotensin system with losartan, blood pressure control, lifestyle change, and statin as needed

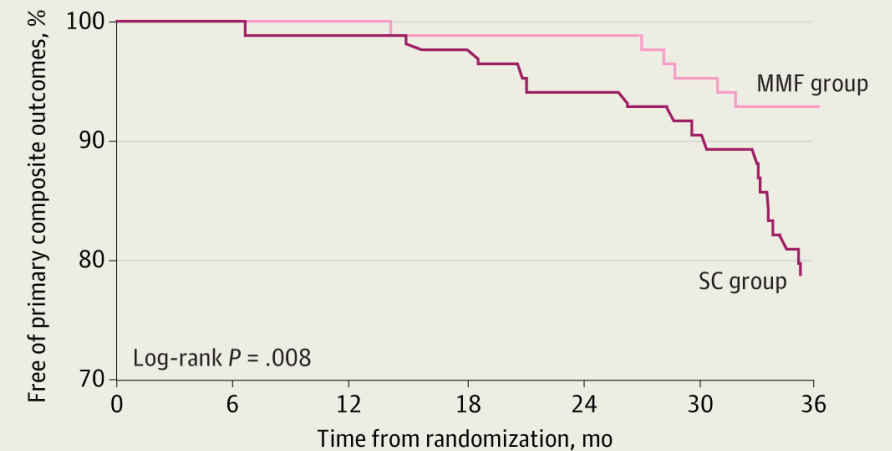


85 Mycophenolate mofetil (MMF) and SC

SC with oral MMF at 1.5 g/d for 12 mo, then 0.75 to 1.0 g/d for >6 mo

FINDINGS

Addition of MMF to SC, compared with SC alone, significantly reduced the risk of the primary composite outcome and delayed the progression of CKD



SETTINGS / LOCATIONS



1 Kidney center in China

PRIMARY OUTCOME

A composite of doubling of serum creatinine, end-stage kidney disease (dialysis, transplant, kidney failure without kidney replacement therapy), or death due to kidney or cardiovascular cause, and progression of chronic kidney disease (CKD)

Composite kidney outcome, MMF group vs SC group:

7.1% vs 21.2%

aHR, 0.23; 95% CI, 0.09-0.63; $P < .001$

Progression of CKD, MMF group vs SC group:

8.2% vs 27.1%

aHR, 0.23; 95% CI, 0.10-0.57; $P < .001$

IgA Nephropathy Patient Baseline Characteristics in the Sparsentan PROTECT Study



Methods & cohort



Patient characteristics
PROTECT study
(NCT03762850)



Compared to
contemporary IgAN
phase 3 trials



IgA nephropathy



Proteinuria $\geq 1\text{g/d}$
Max tolerated
ACEi &/or ARB

IgAN, IgA Nephropathy; ACEi angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

PROTECT study

RCT Double blind
International Multicenter
Active controlled

Sparsentan



Single-molecule
endothelin angiotensin
receptor antagonist

vs

Irbesartan



Active control

Patient characteristics



Patient number
N = 404



Median age
46



Stage 3A CKD
35%



Baseline median
24-h urine protein
1.8g/d



Baseline mean BP
129/82



% on max ACEi
or ARB
63.4%

Europe



53%

Asia pacific



27%

North America



20%



In Asian vs non-Asian regions; higher % of females, lower
BPs & lower % baseline hypertension & related treatment

Barratt J et al. 2023

Visual abstract by:
Sophia Ambruso, DO
 @Sophia_kidney

Conclusion Patient enrollment in PROTECT, with differing racial backgrounds and across CKD stages, will allow for important characterization of the treatment effect of sparsentan in IgAN patients with proteinuria at high risk of kidney failure.

KI REPORTS
Kidney International Reports

Trial* Design

Maximized ACEi/ARB

- ≥12 weeks prior to screening
- ≥50% maximum approved dose

Double-blind treatment
110 weeks, randomized 1:1

4 weeks post cessation
of randomized treatment

**Randomized (1:1) and
received study drug**
(N=404)

- Adults (aged ≥18 years)
- Biopsy-proven IgAN
- UPE ≥1 g/day
- eGFR ≥30 mL/min/1.73 m²

Sparsentan
200 mg/day →
400 mg/day at week 2

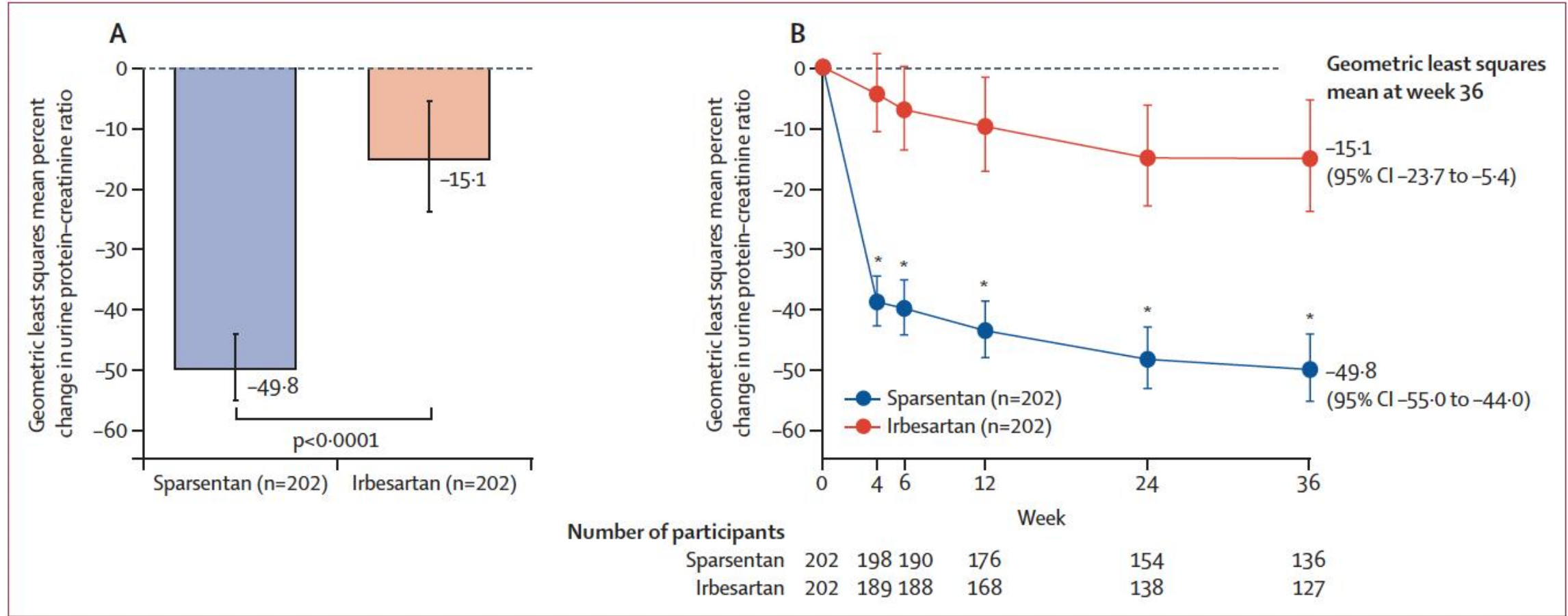
Irbesartan
150 mg/day →
300 mg/day at week 2

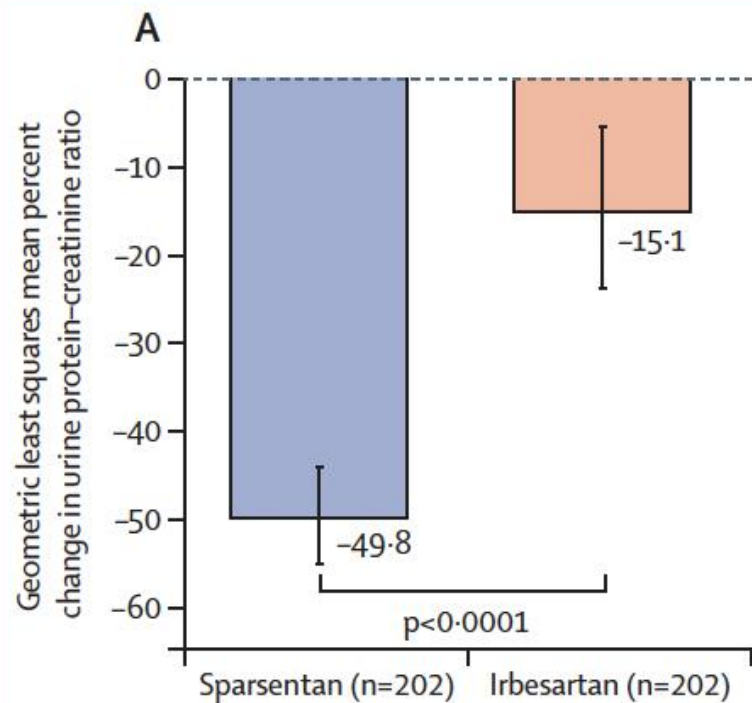
**Study drug
withdrawal period;
resume SOC
ACEi/ARB**



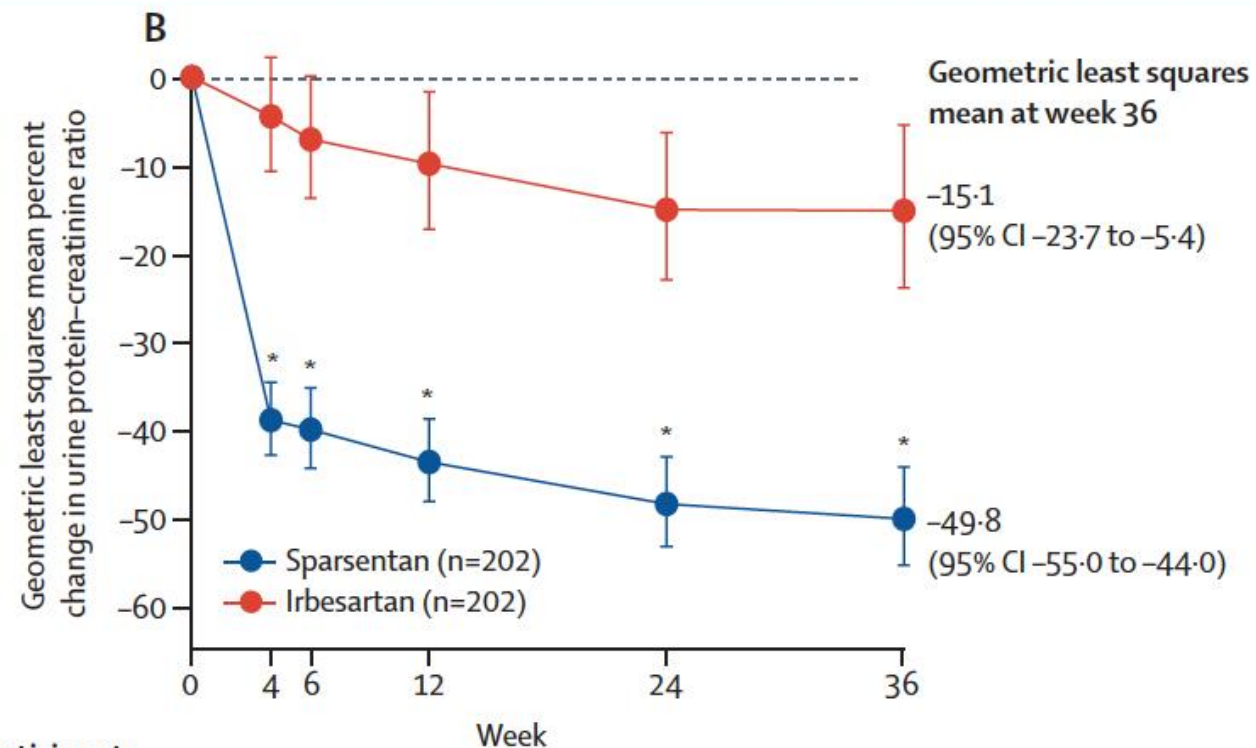
Primary Efficacy Endpoint
Change in UPCR from
baseline to week 36

Key Secondary Efficacy Endpoint
eGFR slope: **chronic** (weeks 6-110)
and **total** (day 1-week 110)



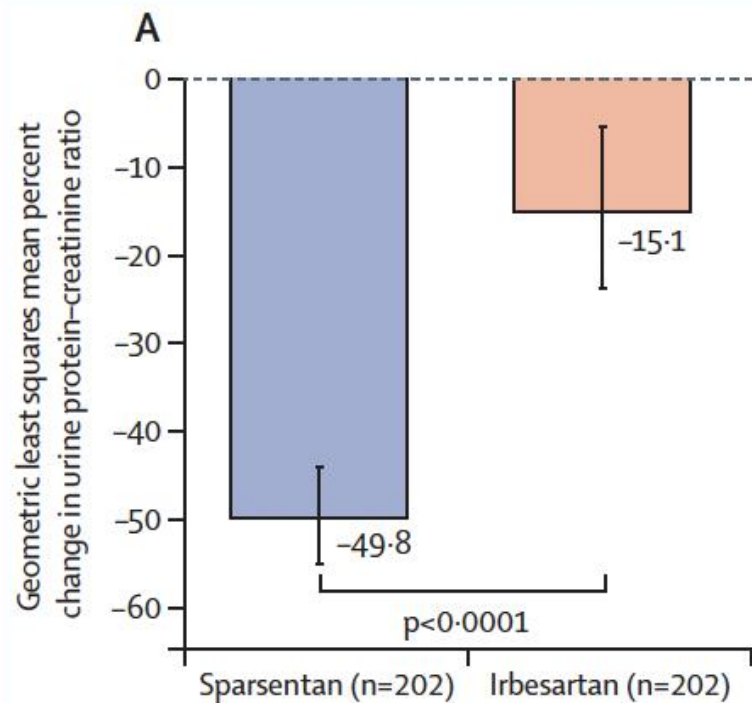


41% RR in proteinuria

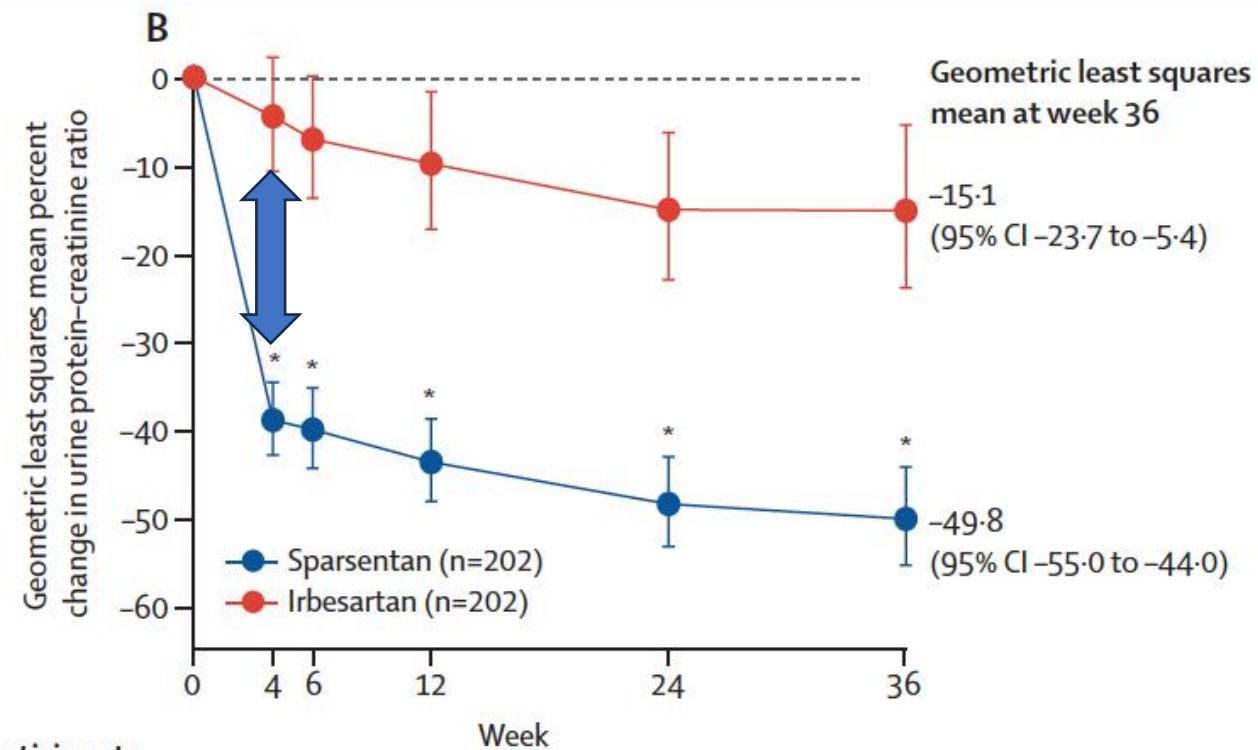


Number of participants

Sparsentan	202	198	190	176	154	136
Irbesartan	202	189	188	168	138	127



41% RR in proteinuria



Number of participants

Sparsentan	202	198	190	176	154	136
Irbesartan	202	189	188	168	138	127

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atrasentan in Patients with IgA Nephropathy

Hiddo J.L. Heerspink, Ph.D.,¹ Meg Jardine, M.B., B.S., Ph.D.,²
Donald E. Kohan, M.D., Ph.D.,³ Richard A. Lafayette, M.D.,⁴ Adeera Levin, M.D.,⁵
Adrian Liew, M.D.,⁶ Hong Zhang, Ph.D.,⁷ Amit Lodha, M.B., B.S.,⁸
Todd Gray, M.S.P.H.,⁹ Yi Wang, Ph.D.,⁸ Ronny Renfurm, M.D.,¹⁰ and
Jonathan Barratt, M.D.,¹¹ for the ALIGN Study Investigators*

N Engl J Med. 2025 Feb 6;392(6):531-543

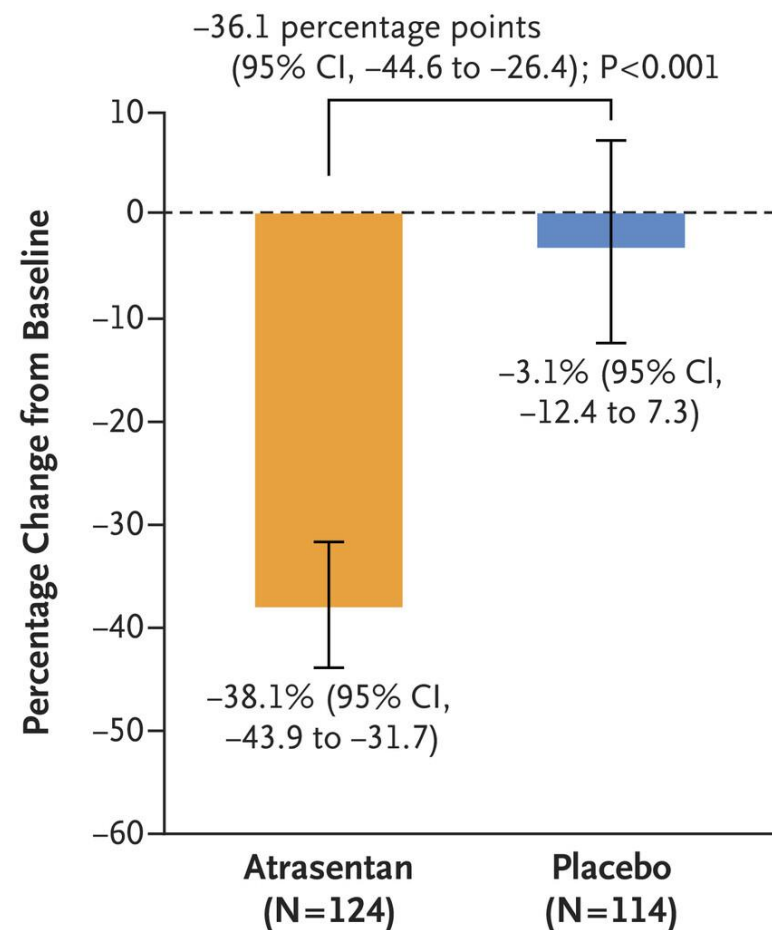


ALIGN – Atrasentan in IgAN

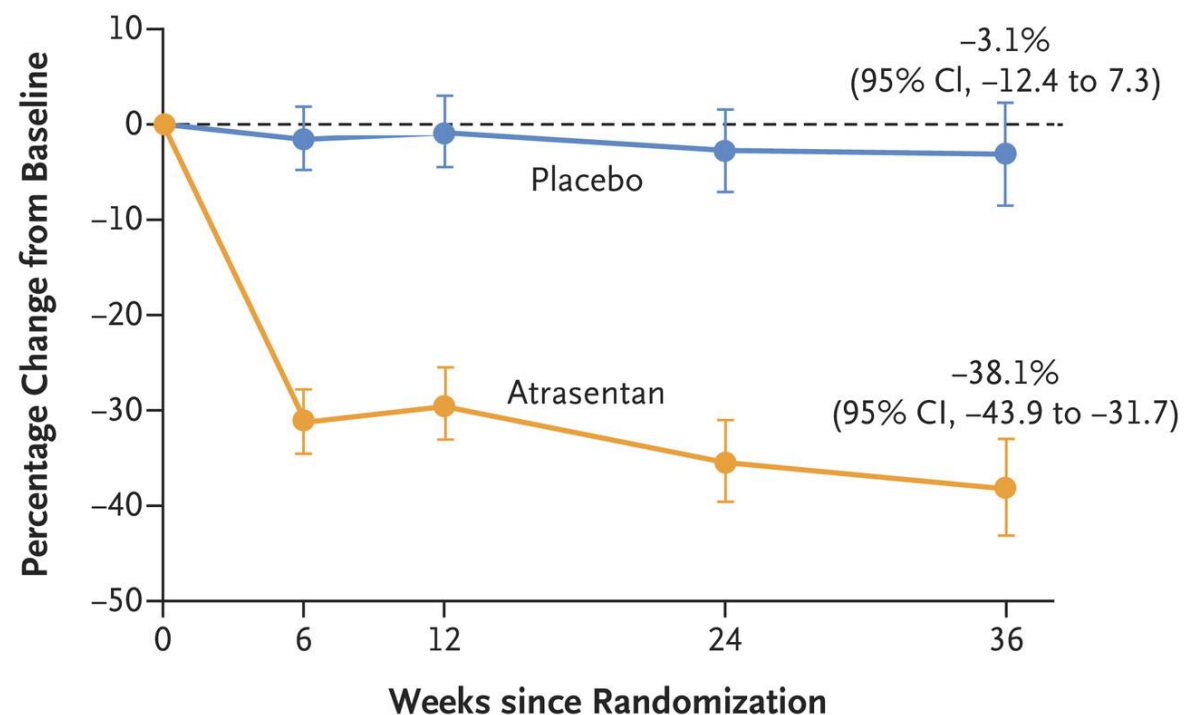
- Phase 3, multinational, double-blind, randomized, controlled trial involving adults with biopsy-proven IgA nephropathy, a total urinary protein excretion of at least 1 g per day, and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m² of body-surface area.
- The primary outcome, assessed at a prespecified interim analysis of data from the first 270 patients in the main stratum, was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36; the change was estimated with the use of a repeated-measures model.
- Fluid retention was reported by 19 of 169 patients (11.2%) in the atrasentan group and in 14 of 170 (8.2%) in the placebo group but did not lead to discontinuation of the trial regimen.
- Lesser LFT issues than with sparsentan.



A Change in 24-Hour Urinary Protein-to-Creatinine Ratio at Week 36



B Change in 24-Hour Urinary Protein-to-Creatinine Ratio at Weeks 6, 12, 24, and 36



No. of Patients

Placebo	132	129	130	126	114
Atrasentan	132	129	125	125	124



B Cell Therapeutics.

- Telitacicept – BAFF / APRIL
- Atacicept – BAFF / APRIL
- Povetacicept – BAFF / APRIL
- Sibeprenlimab – APRIL
- Zigaikibart – APRIL



B Cell Therapeutics.

Telitacicept – BAFF / APRIL

- Phase II trial in China.
- 44 IgAN patients.
- eGFR >35 & proteinuria ≥ 0.75 g/d.
- Telitacicept, 160 mg (n=16) or 240 mg (n=14) subcut every week.
- Vs Placebo (n=14).
- Over 24 weeks.



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 - Vs Placebo (n=14).
 - Over 24 weeks.
- Proteinuria (mean change +/- SD).
 - Placebo, 0.03 +/- 1.09 (-0.66 - 0.60).
 - Telitacicept 160, -0.32 +/- 0.82 (-0.75 - 0.12).
 - Telitacicept 240, -0.89 +/- 0.85.
 - EGFR (mean change +/- SD).
 - Placebo, -5.70 +/- 8.99 (-11.41 - 0.01).
 - Telitacicept 160, 4.32 +/- 9.14 (-0.55 - 9.19).
 - Telitacicept 240, 2.34 +/- 5.21 (-0.67 - 5.35).
 - SAEs (percentage).
 - Placebo, 7.10.
 - Telitacicept 160, 6.30.
 - Telitacicept 240, 14.40.



B Cell Therapeutics.

Telitacicept – BAFF / APRIL

- Phase II RCT.
- 24 IgAN patients.
- eGFR >35 & proteinuria $\geq$ 0.75 g/d.
- Telitacicept, 160 mg (n=9) or 240 mg (n=9).
- Vs Placebo (n=8).
- Over 24 weeks.



B Cell Therapeutics.

Telitacicept – BAFF / APRIL

- Phase II RCT.
 - 24 IgAN patients.
 - eGFR >35 & proteinuria ≥ 0.75 g/d.
 - Telitacicept, 160 mg (n=9) or 240 mg (n=9).
 - Vs Placebo (n=8).
 - Over 24 weeks.
- Gd-IgA1, mean decrease % (95% CI).
 - Placebo, Ref.
 - Telitacicept 160, 43.9% (29.8%, 55.1%).
 - Telitacicept 240, 50.4% (38.6%, 59.9%).
 - IgG-IgA IC, mean decrease % (95% CI).
 - Placebo, Ref.
 - Telitacicept 160, 31.7% (14.4%, 45.5%).
 - Telitacicept 240, 42.7% (29.5%, 53.4%).
 - Poly-IgA IC, mean decrease % (95% CI).
 - Placebo, Ref.
 - Telitacicept 160, 41.3% (6.5%, 63.1%).
 - Telitacicept 240, 67.2% (48.5%, 79.1%).



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Sibeprenlimab in IgA Nephropathy — Interim Analysis of a Phase 3 Trial

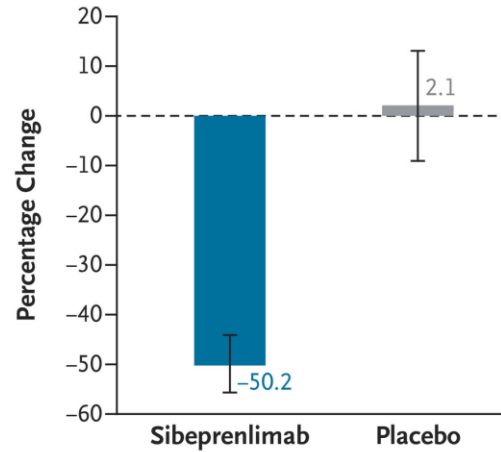
V. Perkovic,¹ H. Trimarchi,² V. Tesar,³ R. Lafayette,⁴ M.G. Wong,⁵ J. Barratt,⁶ Y. Suzuki,⁷ A. Liew,⁸ H. Zhang,⁹ K. Carroll,¹⁰
V. Jha,¹¹⁻¹³ A. Quevedo,¹⁴ S.H. Han,¹⁵ M. Praga,¹⁶ B. Chacko,¹⁷ M. Sahay,¹⁸ C.K. Cheung,⁶ L. Kooienga,¹⁹ M. Walsh,^{20,21}
J. Xia,²² C. Fajardo,²² L. Shah,²² J. Hafkin,²² and D.V. Rizk,²³ for the VISIONARY Trial Investigators Group*



VISIONARY Trial, Sibeprenlimab, APRIL inhibitor

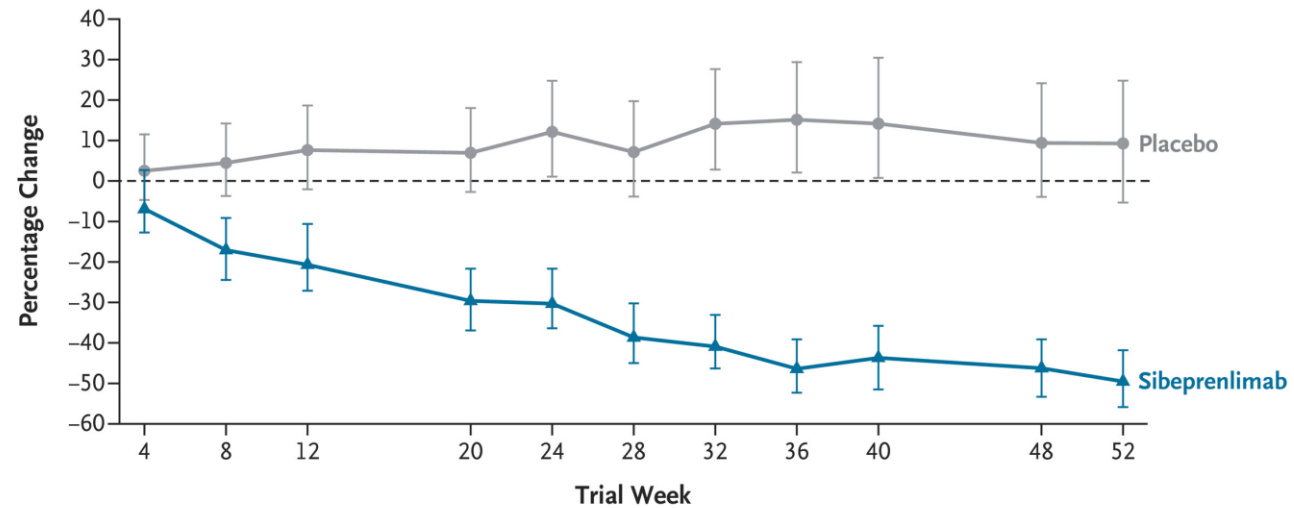
- Biopsy-confirmed IgA nephropathy in a 1:1 ratio to receive either subcutaneous sibeprenlimab at a dose of 400 mg or placebo administered every 4 weeks for 100 weeks. The primary end point for this interim analysis was the 24-hour urinary protein-to-creatinine ratio at 9 months as compared with baseline. The key secondary end point, to be reported at trial completion, is the annualized slope of estimated glomerular filtration rate over 24 months.
- 510 patients, median UPCs ~1.3, ~98% on RAASi and ~35% on SGLT2i

A Change in 24-Hr UPCR at Month 9



	Sibeprenlimab	Placebo
Baseline		
No. of patients	152	168
24-Hr UPCR — GM (GSD)	1.33 (1.74)	1.32 (1.62)
Month 9 (week 40)		
No. of patients	145	161
24-Hr UPCR — GM (GSD)	0.65 (2.34)	1.31 (2.03)

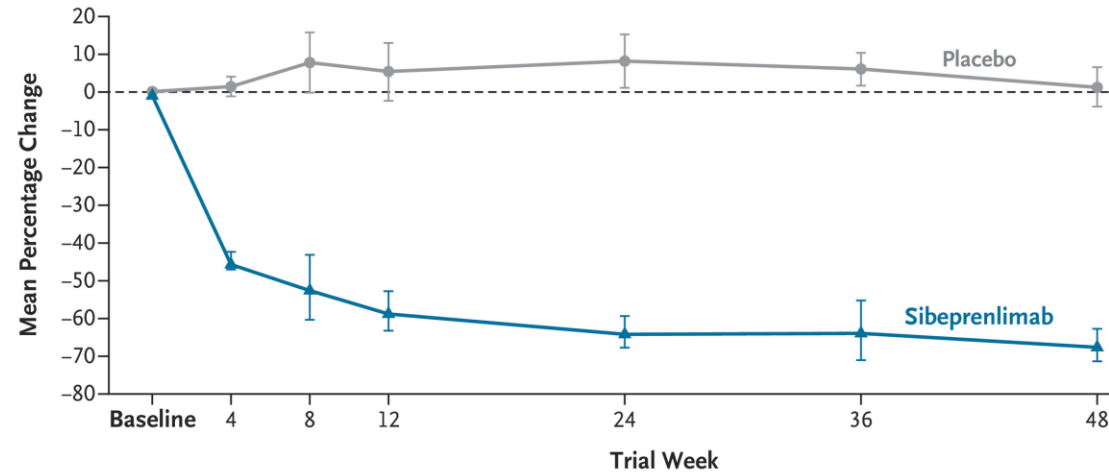
B Least-Squares Geometric Mean Change in Spot UPCR from Baseline



No. of Patients

Placebo	145	145	151	146	144	151	150	142	120	120	91
Sibeprenlimab	127	123	127	123	127	127	126	124	106	101	75

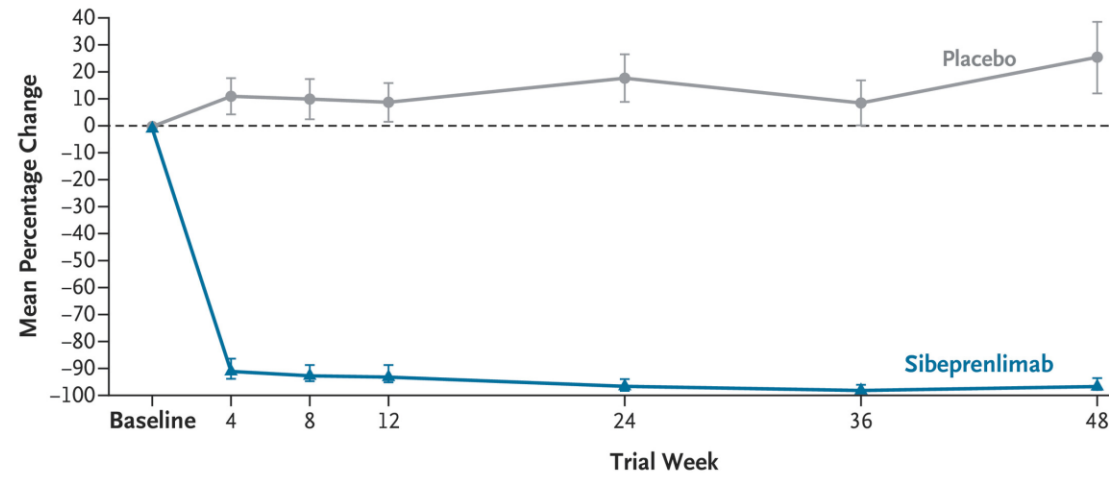
A Change in Serum GD-IgA1 Level from Baseline



No. of Patients

Placebo	248	244	238	240	235	176	125
Sibeprenlimab	255	248	244	244	241	159	108

B Change in APRIL Level from Baseline



No. of Patients

Placebo	244	239	234	238	233	174	122
Sibeprenlimab	252	245	242	239	238	157	106

A Phase 3 Trial of Atacicept in Patients with IgA Nephropathy

Richard Lafayette, M.D.,¹ Sean J. Barbour, M.D.,² Robert M. Brenner, M.D.,³
Kirk N. Campbell, M.D.,⁴ Tom Doan,³ Necmi Eren, M.D.,⁵ Jürgen Floege, M.D.,⁶
Vivekanand Jha, M.B., B.S., M.D., D.M.,⁷ Beom Seok Kim, M.D., Ph.D.,⁸
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Dana V. Rizk, M.D.,¹⁶ Hitoshi Suzuki, M.D., Ph.D.,¹⁷
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Xuelian Wei, Ph.D.,³ Hong Zhang, M.D., Ph.D.,²⁰ and Jonathan Barratt, Ph.D.,²¹
for the ORIGIN Phase 3 Trial Investigators*

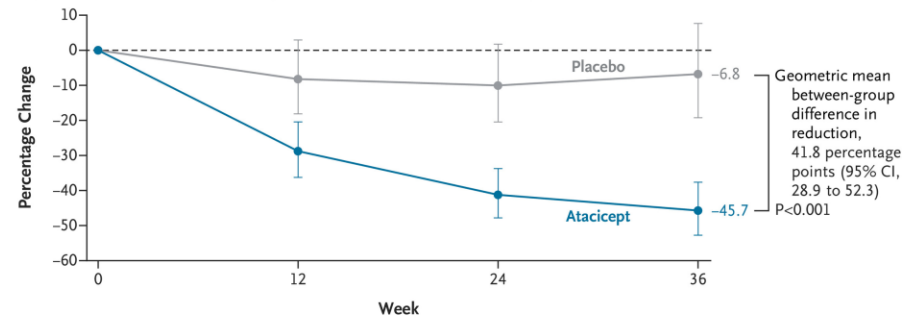
ABSTRACT

Atacicept, BAFF/APRIL inhibitor

- Patients with IgA nephropathy in a 1:1 ratio received atacicept at a dose of 150 mg once weekly, administered subcutaneously by patients at home, or matching placebo. The primary end point was the percentage change from baseline in the 24-hour urinary protein-to-creatinine ratio at week 36.
- 203 patients, mean UPC ~1.7, 99% on RAASi



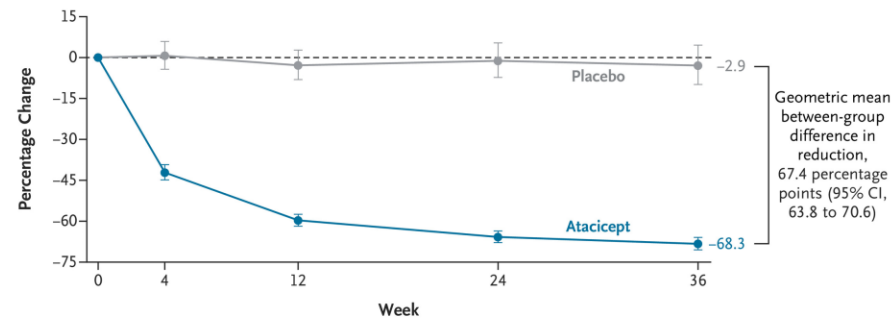
A Change from Baseline in 24-Hr Urinary Protein-to-Creatinine Ratio through Week 36



No. of Patients

Placebo	97	96	97	95
Atacicept	106	104	104	103

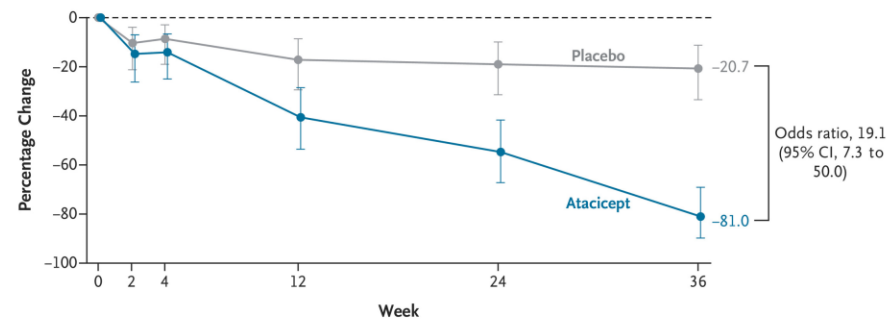
B Change from Baseline in Galactose-Deficient IgA1 through Week 36



No. of Patients

Placebo	97	93	93	94	95
Atacicept	104	103	96	100	101

C Change from Baseline in Percentage of Patients with Hematuria through Week 36



No. of Patients

Placebo	58	58	58	58	58
Atacicept	64	61	64	64	63

Complement Blockade.

Reduce the burden of the downstream complement activation.

- Avacopan – C5a receptor antagonist
- Cemdisiran – C5 in liver
- Iptacopan – Factor B inhibitor
- Narsoplimab – MASP2 inhibitor
- Ravulizumab – C5 inhibitor
- Pegcetacoplan – C3 inhibitor



Results of a randomized double-blind placebo-controlled Phase 2 study propose iptacopan as an alternative complement pathway inhibitor for IgA nephropathy.

kidney
INTERNATIONAL



Methods

PHASE 2



Proof of concept,
dose-ranging
study



Double-blind



Randomized



Biopsy-confirmed
primary IgA
nephropathy

Intervention



Iptacopan versus placebo
(administered orally, twice daily)

Part 1 (3-month treatment)



(N=46)

Iptacopan 10 mg
Iptacopan 50 mg
Iptacopan 200 mg
Placebo

Part 2 (6-month treatment)



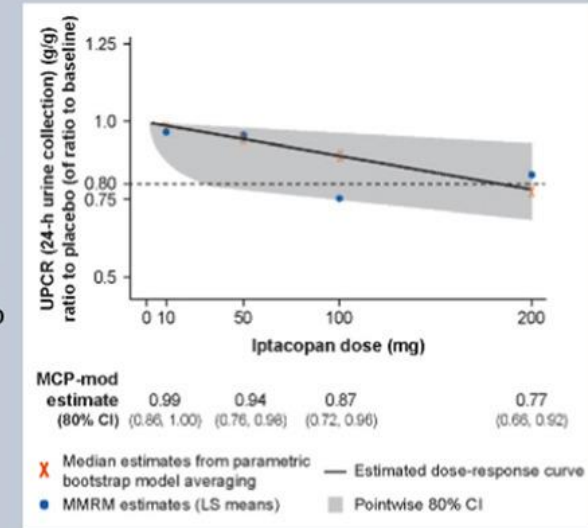
(N=66)

Iptacopan 10 mg
Iptacopan 50 mg
Iptacopan 100 mg
Iptacopan 200 mg
Placebo

Findings

Primary analysis:

- Statistically significant dose-response effect observed ($P=0.038$), with a 23% (80% CI: 8–34) reduction in UPCR from baseline achieved with iptacopan 200 mg vs placebo at 3 months



Secondary analysis:

- Strong inhibition of several biomarkers of alternative complement activity (plasma Bb, Wieslab assay in serum, and urinary sC5b-9) observed; maximal inhibition observed with iptacopan 200 mg that was sustained through month 6

Zhang, 2023

CONCLUSION

This is the first study to show that selective inhibition of alternative pathway with iptacopan 200 mg results in a clinically meaningful reduction in proteinuria in patients with IgA nephropathy



The NEW ENGLAND JOURNAL *of* MEDICINE

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FEBRUARY 6, 2025

VOL. 392 NO. 6

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

V. Perkovic,¹ J. Barratt,² B. Rovin,³ N. Kashihara,⁴ B. Maes,⁵ H. Zhang,⁶ H. Trimarchi,⁷ D. Kollins,⁸ O. Papachristofi,⁸
S. Jacinto-Sanders,⁸ T. Merkel,⁸ N. Guerard,⁸ R. Renfurm,⁸ T. Hach,⁸ and D.V. Rizk,⁹ for the APPLAUSE-IgAN Investigators*

N Engl J Med. 2025 Feb 6;392(6):531-543

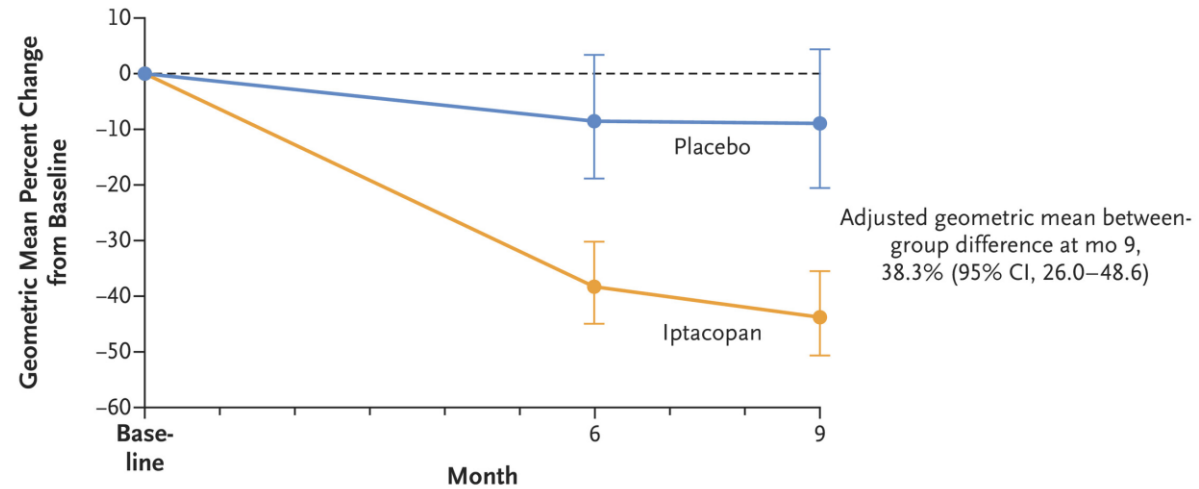


APPLAUSE-IgAN – Iptacopan in IgAN

- Phase 3, double-blind, randomized, placebo-controlled trial, we enrolled adults with biopsy-confirmed IgA nephropathy and proteinuria (defined as a 24-hour urinary protein-to-creatinine ratio of ≥ 1 [with protein and creatinine both measured in grams]) despite optimized supportive therapy.
- Patients were randomly assigned, in a 1:1 ratio, 222 patients in the iptacopan group and 221 in the placebo group, to receive oral iptacopan (200 mg) or placebo twice daily for 24 months while continuing to receive supportive therapy.
- The primary objective of this prespecified interim analysis was to assess the efficacy of iptacopan as compared with that of placebo in reducing proteinuria at month 9.



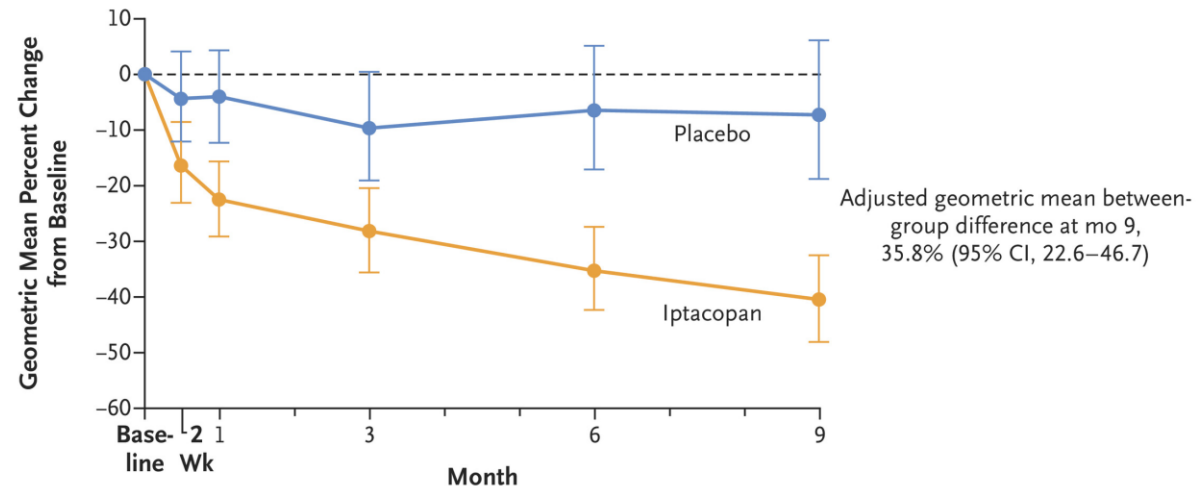
A Change in 24-Hr Urinary Protein-to-Creatinine Ratio



No. of Patients

Placebo	125	112	106
Iptacopan	125	115	118

B Change in Protein-to-Creatinine Ratio from First Morning Urine Sample



No. of Patients

Placebo	123	120	114	113	110	104
Iptacopan	124	116	116	119	114	115



What Should The Approach To IgAN Be As Of Today?

- Goal is to reduce proteinuria to <0.3 grams/day
- Incident versus post-RAASi/SGLT2i proteinuria as the trigger? Insurance approval proteinuria threshold is an issue.
- Reduce the IgAN-associated elevation in galactose-deficient IgA
 - Glucocorticoids – Nefecon or prednisone or prednisone+MMF
 - APRIL/BAFF inhibitor – sibeprenlimab, atacicept, and povetacicept are now FDA-approved
- Reduce the IgAN-associated complement activation
 - Iptacopan – REMS program
- Target IgAN-associated nephron loss:
 - Initiate RAASi and SGLT2i (DAPA-CKD)
 - Consider sparsentan (REMS program for LFTs) or atrasentan

The Development and Demise of Avacopan

BRIEF COMMUNICATION

www.jasn.org

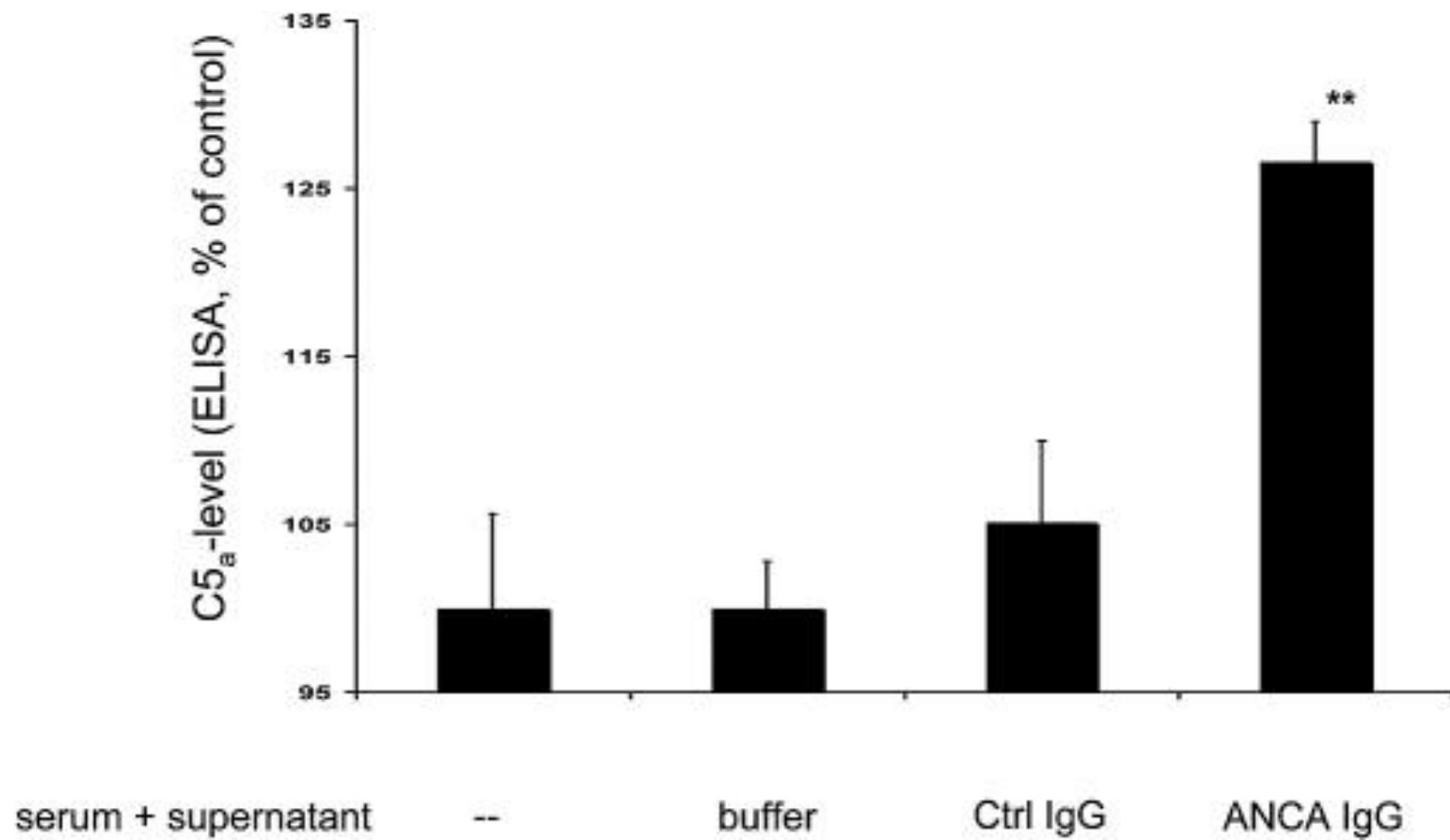
C5a Receptor (CD88) Blockade Protects against MPO-ANCA GN

Hong Xiao,^{*†} Daniel J. Dairaghi,[‡] Jay P. Powers,[‡] Linda S. Ertl,[‡] Trageen Baumgart,[‡] Yu Wang,[‡] Lisa C. Seitz,[‡] Mark E.T. Penfold,[‡] Lin Gan,[§] Peiqi Hu,^{*†} Bao Lu,[§] Norma P. Gerard,^{||} Craig Gerard,^{||} Thomas J. Schall,[‡] Juan C. Jaen,[‡] Ronald J. Falk,^{*†} and J. Charles Jennette^{*†}

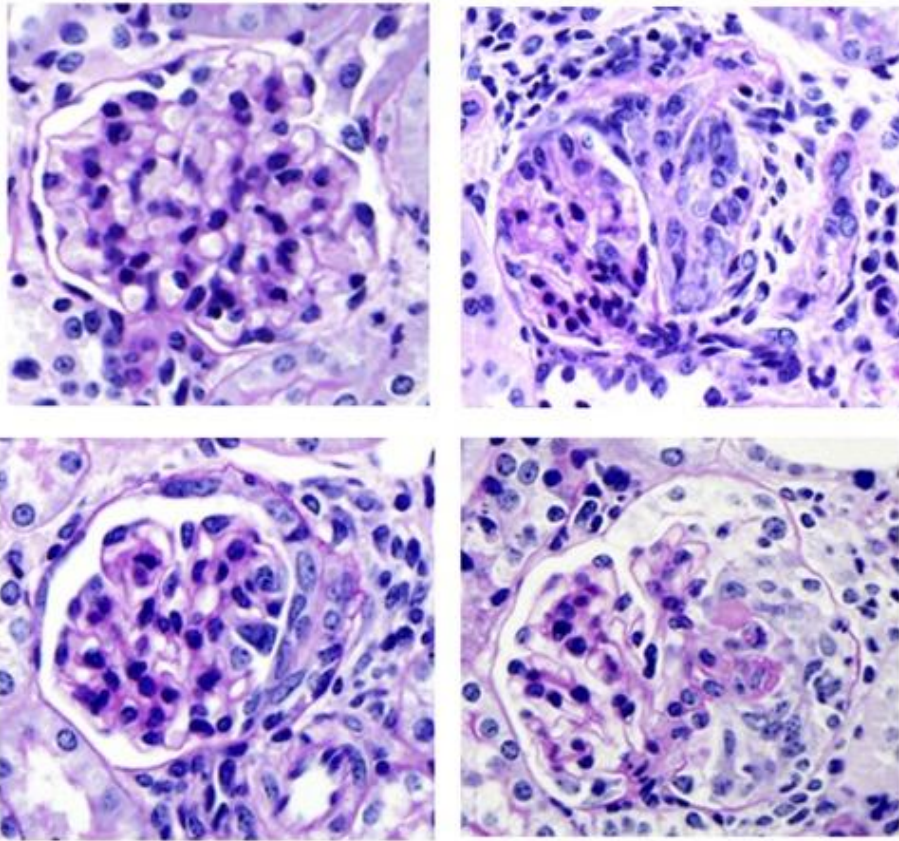
^{*}Department of Pathology and Laboratory Medicine and [†]UNC Kidney Center, University of North Carolina, Chapel Hill, North Carolina; [‡]ChemoCentryx, Inc., Mountain View, California; [§]Department of Ophthalmology, University of Rochester, Rochester, New York; and ^{||}Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

J Am Soc Nephrol. 2014 Feb;25(2):225-31



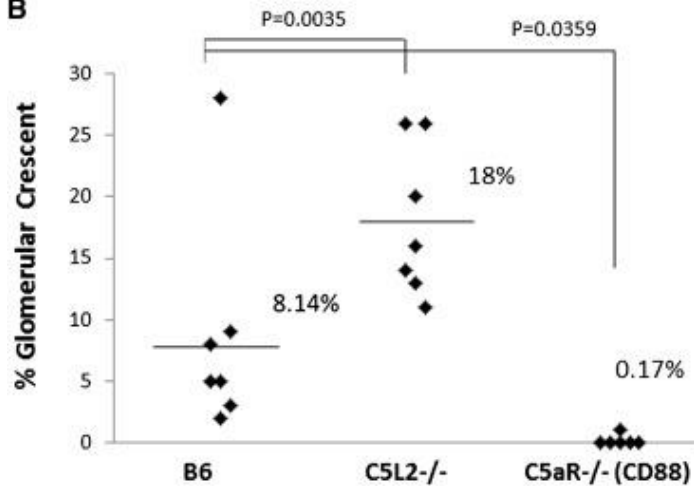


A

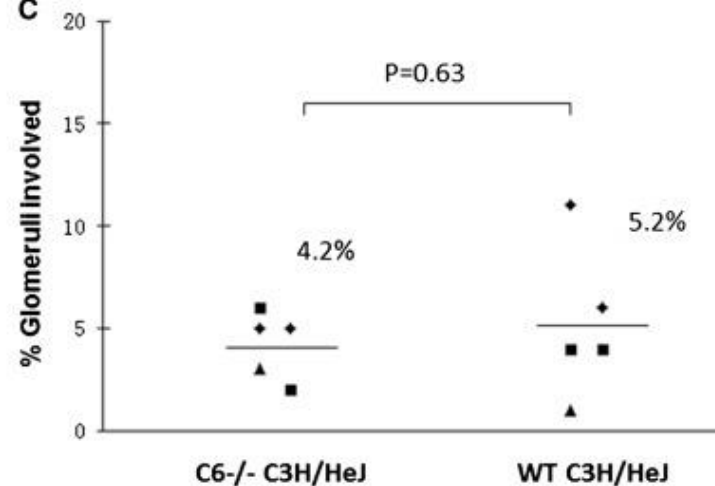


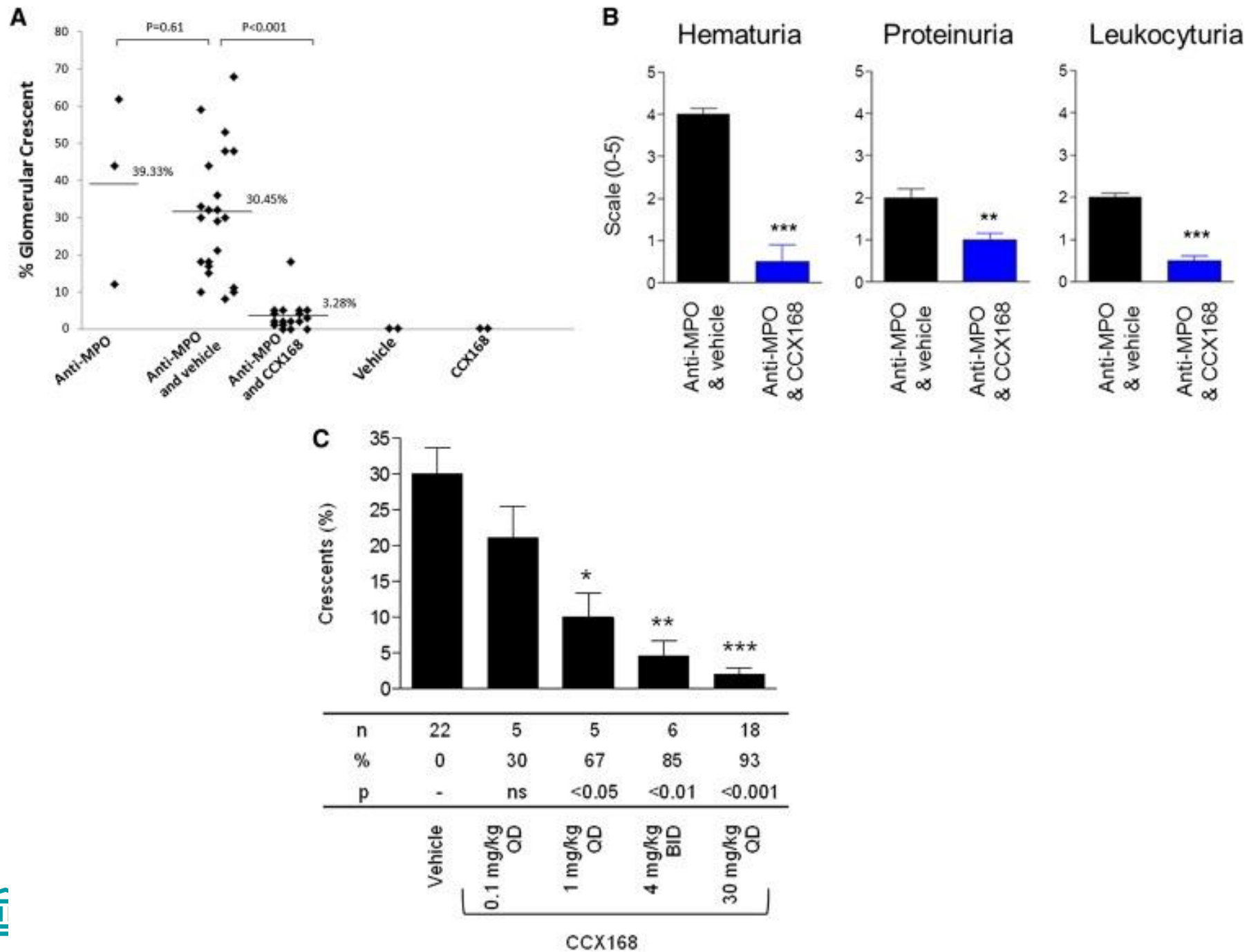
**C5aR deficiency ameliorates,
C5L2 deficiency enhances,
and C6 deficiency has no
effect on
anti-MPO–induced GN.**

B



C





**CCX168
is
Avacopan**

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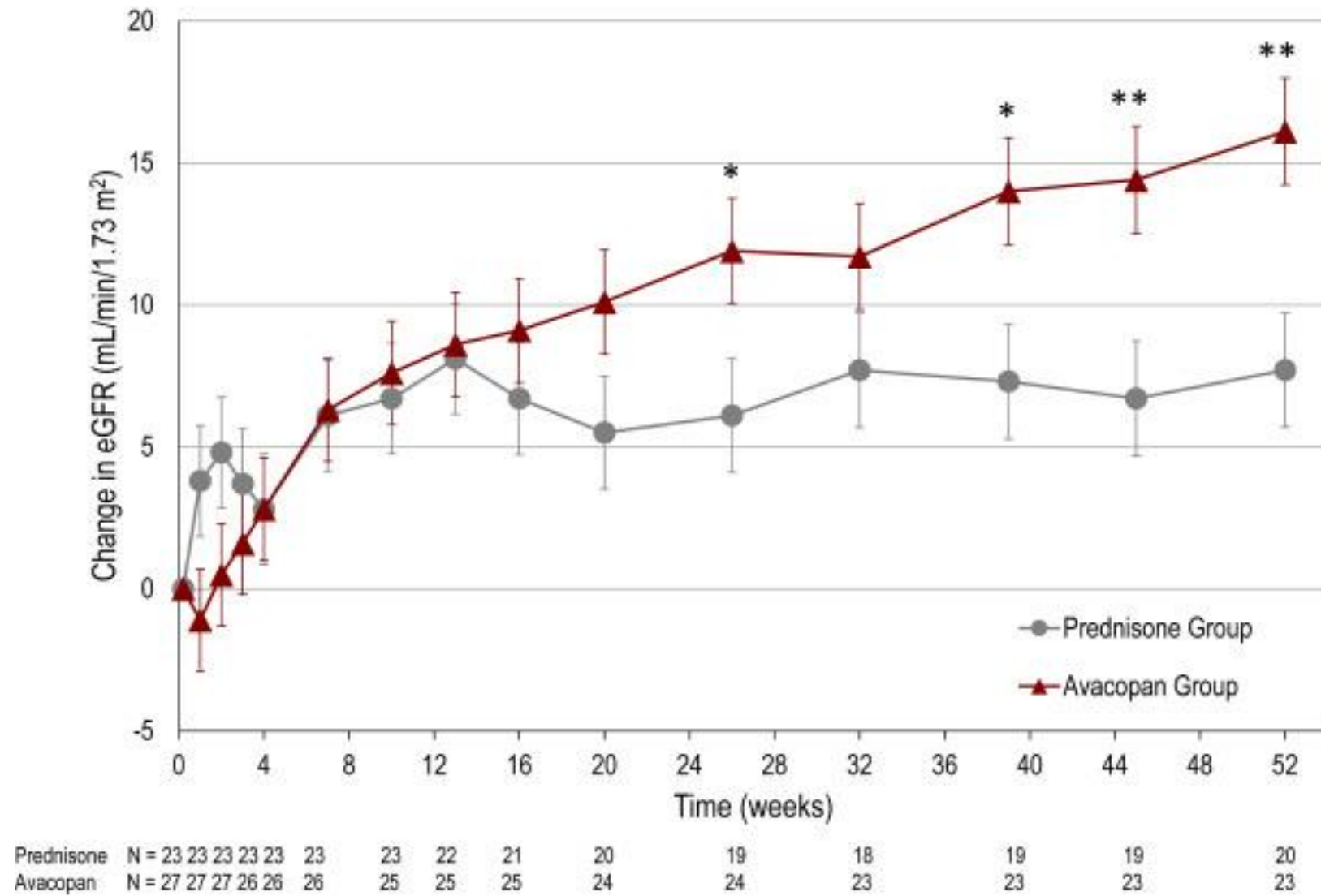
FEBRUARY 18, 2021

VOL. 384 NO. 7

Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D.,
for the ADVOCATE Study Group*





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RESEARCH LETTER

Avacopan in Anti-Neutrophil Cytoplasmic Autoantibodies–Associated Vasculitis in a Real-World Setting



Jonas Zimmermann^{1,2,7}, Janis Sonnemann^{1,2,7}, Wolfram J. Jabs^{3,7}, Ulf Schönermarck⁴, Volker Vielhauer⁴, Markus Bieringer⁵, Udo Schneider⁶, Ralph Kettritz^{1,2} and Adrian Schreiber^{1,2}

¹Department of Nephrology and Medical Intensive Care, Charité - Universitätsmedizin Berlin, Germany; ²Experimental and Clinical Research Center, Charité - Universitätsmedizin Berlin and Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany; ³Department of Nephrology, Vivantes Klinikum im Friedrichshain, Berlin, Germany; ⁴Department of Medicine IV, Division of Nephrology, LMU University Hospital, LMU Munich, Germany; ⁵Department of Cardiology and Nephrology, Helios Klinikum Berlin - Buch, Germany; and ⁶Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Germany

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CLINICAL RESEARCH

Systematic Review of Efficacy and Safety of Avacopan in Real-World Clinical Practice



Ilay Berke¹, Felix Keller¹, Clemens Untersulzner¹, Jae Il Shin^{2,3,4}, Peong Gang Park², Sarah Soyeon Oh⁵, Jasper Callemeyn^{1,6} and Andreas Kronbichler^{1,7}

¹Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck, Austria; ²Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea; ³The Center for Medical Education Training and Professional Development in Yonsei-Donggok Medical Education Institute, Seoul, Republic of Korea; ⁴Severance Underwood Meta-research Center, Institute of Convergence Science, Yonsei University, Seoul, Republic of Korea; ⁵Institute of Global Engagement and Empowerment, Yonsei University, Seoul, Republic of Korea; ⁶Nephrology and Renal Transplantation Research Group, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium; and ⁷Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

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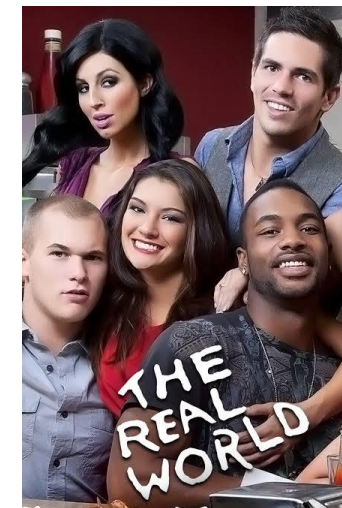
CLINICAL RESEARCH

Real-World Experience With Avacopan in Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis

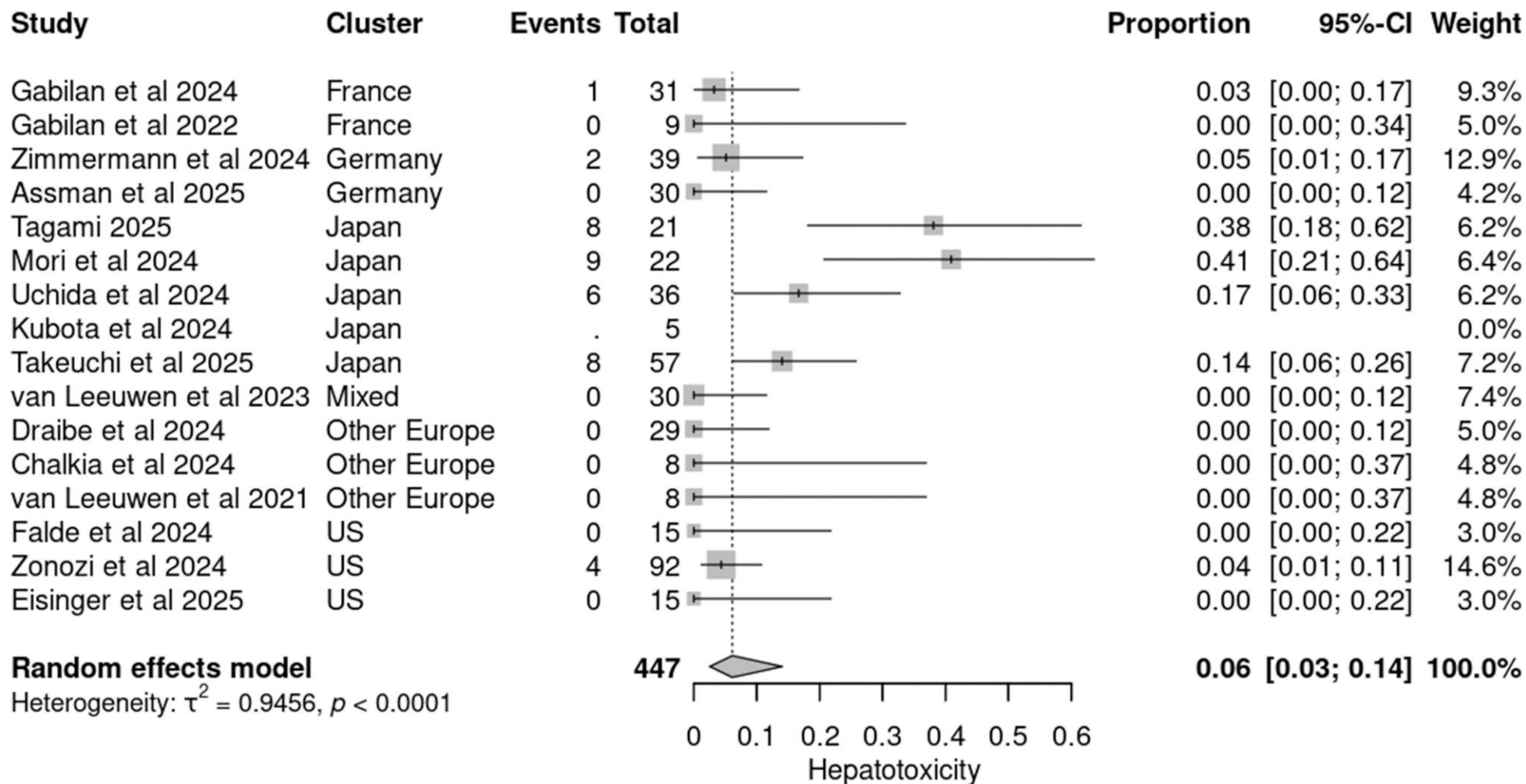


Reza Zonozi^{1,2,16}, Faten Aqeel^{3,16}, Dustin Le³, Frank B. Cortazar⁴, Jugal Thaker⁵, Maria Jose Zabala Ramirez⁶, Sebastian Eduardo Sattui Cortes⁷, Rose Mary Attieh⁸, Madeline Chung⁹, David H. Bulbin¹⁰, Aisha Shaikh¹¹, Karina Guaman¹², Julia Ford¹³, Colin Diffie¹¹, Ora Gewurz-Singer¹³, Gabriel Sauvage¹⁴, Anushya Jeyabalan¹⁴, Abdallah Geara⁵, Isabelle Ayoub⁹, Andrew Bomback¹², Lara L. Khoury^{8,15}, Jason C. George¹⁰, Kenar D. Jhaveri⁸, Vimal Kumar Derebail⁶, John L. Niles¹⁴ and Duvuru Geetha³

¹Nephrology Associates of Northern Virginia, Fairfax, Virginia, USA; ²Inova Fairfax Hospital, Falls Church, Virginia, USA; ³Johns Hopkins Hospital, Baltimore, Maryland, USA; ⁴New York Nephrology Vasculitis and Glomerular Center, Albany, New York, USA; ⁵University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; ⁶University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; ⁷University of Pittsburgh, Pittsburgh, Pennsylvania, USA; ⁸Northwell Health, New Hyde Park, NY Division of Kidney Diseases and Hypertension, Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, USA; ⁹Ohio State University, Wexner Medical Center, Columbus, Ohio, USA; ¹⁰Geisinger Health Medicine, Danville, Pennsylvania, USA; ¹¹Washington University in St. Louis, St. Louis, Missouri, USA; ¹²Columbia University Medical Center, New York, New York, USA; ¹³University of Michigan, Ann Arbor, Michigan, USA; ¹⁴Vasculitis and Glomerulonephritis Center, Massachusetts General Hospital, Boston, Massachusetts, USA; and ¹⁵Northwell Health, New Hyde Park, New York, Division of Rheumatology, Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, USA



Hepatotoxicity; Marked Increase in Japan



RESEARCH

Open Access



Efficacy and safety of avacopan in antineutrophil cytoplasmic autoantibody-associated vasculitis: a retrospective cohort study in Japan

Genri Tagami^{1†}, Makoto Yamaguchi^{1†}, Hirokazu Sugiyama¹, Hiroshi Kinashi¹, Kentaro Imai¹, Keisuke Kamiya¹, Takayuki Katsuno^{1,2}, Takahiro Imaizumi³, Shogo Banno¹, Yasuhiko Ito¹ and Takuji Ishimoto^{1*}

Abstract

Background Avacopan, an oral C5a receptor antagonist, demonstrated efficacy as an alternative to glucocorticoid therapy in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in the phase 3 ADVOCATE trial. However, limited real-world data exist on the outcomes and experiences associated with avacopan use for AAV in Japan.

Methods We performed a single-centre retrospective analysis and evaluated 21 patients with newly diagnosed or relapsed AAV who received avacopan. The co-primary outcomes were clinical remission at 6 and 12 months.

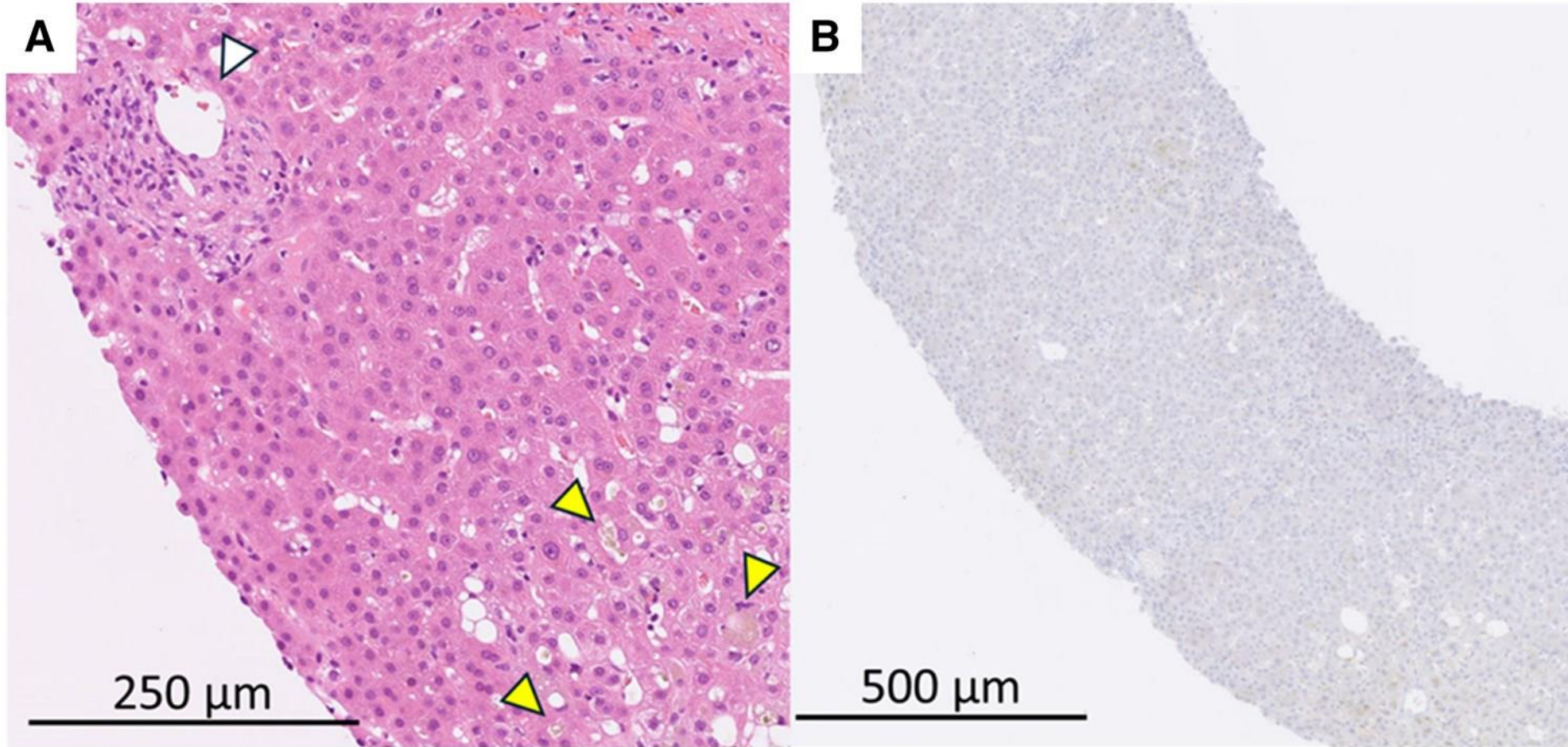
Results Among the 21 patients, 20 (95.2%) achieved clinical remission at 6 months, and 19 (90.4%) sustained remission at 12 months. The median time from initiation of immunosuppressive therapy to the start of avacopan was 12 days (interquartile range, 5–26). Adverse events were reported in 10 patients (47.6%), with elevated liver enzyme levels observed in eight patients (38.1%) as the most frequent complication. Avacopan was discontinued in nine patients (42.9%). Despite early discontinuation, these patients achieved comparable rates of clinical remission at 6 months, sustained remission at 12 months, and experienced a reduction in glucocorticoid doses relative to those who continued avacopan.

Conclusions A high incidence of adverse events, particularly liver enzyme elevation, and frequent early discontinuations of avacopan were observed. Nevertheless, favourable clinical outcomes and reduced glucocorticoid doses were achieved regardless of avacopan discontinuation. Further studies are warranted to validate the optimal use of avacopan in clinical practice.

Keywords Antineutrophil cytoplasmic autoantibody-associated vasculitis, Avacopan, Efficacy, Remission, Safety

8 out of 21 patients developed avacopan-associated liver injury....

Vanishing Bile Duct Syndrome



Vanishing Bile Duct Syndrome

Characterized by a paucity of intrahepatic bile ducts and by eventual cholestasis and biliary cirrhosis.

Causes include:

- PBC, primary sclerosing cholangitis, autoimmune hepatitis
- graft-versus-host disease, chronic liver allograft rejection
- ischemia, intrahepatic chemotherapy
- drugs (e.g., ampicillin, amoxicillin, avacopan, flucloxacillin, erythromycin, tetracycline, doxycycline, cotrimoxazole)
- HIV infection, sarcoidosis, idiopathic or paraneoplastic bile duct paucity, histiocytosis, Hodgkin's lymphoma



FDA Shoe Drop #1

In January 2026, the FDA requested that Amgen withdraw Tavneos from the US market due to concerns over how 9 of the 331 study participants were assessed for the primary endpoint in ADVOCATE.

The Agency also questioned whether the drug's benefits outweighed its risks, citing the known risk of hepatotoxicity. The “real-world” experience (Cortazar et al, Zonozi et al, and Zimmerman et al) reports improved renal outcomes with avacopan in patients with severe renal involvement.



FDA Shoe Drop #2

- FDA advisory 3/31/26 re cases of severe liver toxicity.
- “A total of 74 cases reported a serious outcome, including hospitalization (n=54) and death (n=8). A total of 60 cases provided laboratory information to determine the initial pattern of liver injury; the majority (n=38) had a cholestatic or mixed pattern often marked by substantial elevations in ALP and total bilirubin. A total of 73 cases provided time from avacopan initiation to **drug-induced liver injury** onset, and the median time-to-onset was 46 days (range 22 to 140 days). Most cases (n=66) were reported from Japan, followed by the United States (n=5), Europe (n=4), and Canada (n=1).”



Liver Toxicity FDA (cont'd)

“Of the 76 cases, 7 reported biopsy-confirmed “vanishing bile duct syndrome” (VBDS) as a complication of DILI with reasonable evidence of a causal association with avacopan use. All cases reported hospitalization (n=7), of which 3 had a fatal outcome. The initial pattern of liver injury was cholestatic or mixed in 4 cases and hepatocellular in 3 cases. The median time from avacopan initiation to DILI onset among the 7 cases was 46 days (range 33 to 59 days). Cases were reported from Japan (n=6) and Canada (n=1)”.



Obinutuzumab in SLE Nephritis and Membranous GN

- In the LUNAR trial of rituximab in SLE nephritis, patients who successfully achieved B cell depletion DID respond.
- Rituximab is internalized from the plasma membrane in SLE nephritis B cells → B cell resistance. There may be a genetic component to this resistance.
- Obinutuzumab is a type II anti-CD20 mAb → greater cell-mediated cytotoxicity, more effective B cell depletion in circulation and in tissues.
- Very promising Phase 2 NOBILITY trial in SLE nephritis 2022 → adoption at BWH for SLE nephritis at that time.

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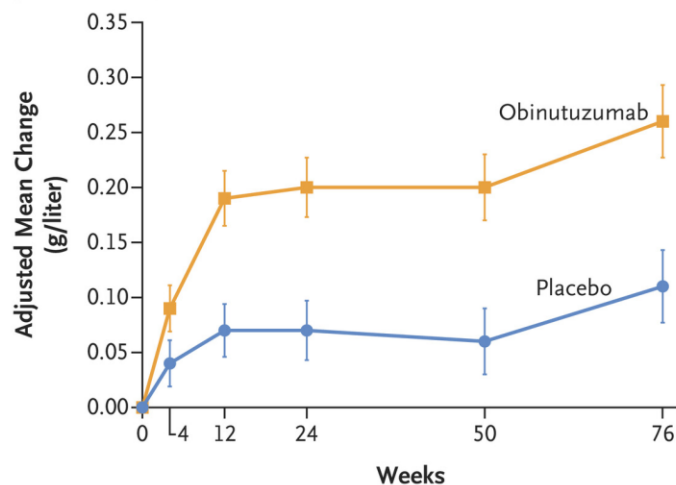
APRIL 17, 2025

VOL. 392 NO. 15

Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

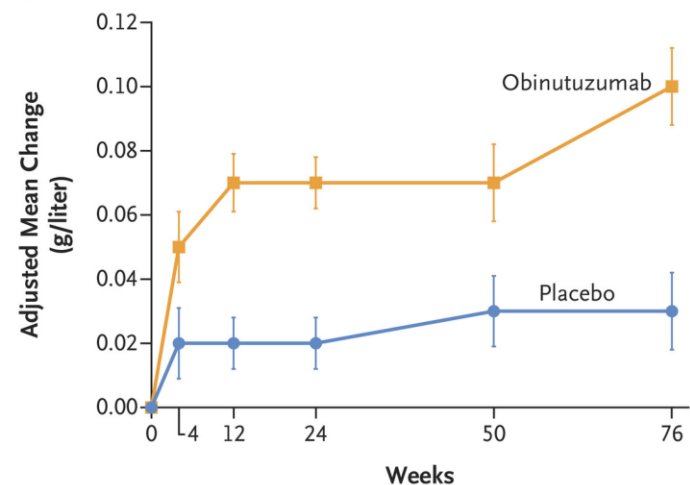
R.A. Furie,¹ B.H. Rovin,² J.P. Garg,³ M.B. Santiago,^{4,6} G. Aroca-Martínez,^{7,8} A.E. Zuta Santillán,⁹ D. Alvarez,¹⁰
C. Navarro Sandoval,¹¹ A.M. Lila,¹² J.A. Tumlin,¹³ A. Saxena,¹⁴ F. Irazoque Palazuelos,¹⁵ H. Raghu,³ B. Yoo,³
I. Hassan,¹⁶ E. Martins,¹⁷ H. Sehgal,¹⁷ P. Kirchner,¹⁷ J. Ross Terres,³ T.A. Omachi,³ T. Schindler,¹⁷
W.F. Pendergraft III,³ and A. Malvar,¹⁸ for the REGENCY Trial Investigators*

A Change in C3 Complement Level from Baseline



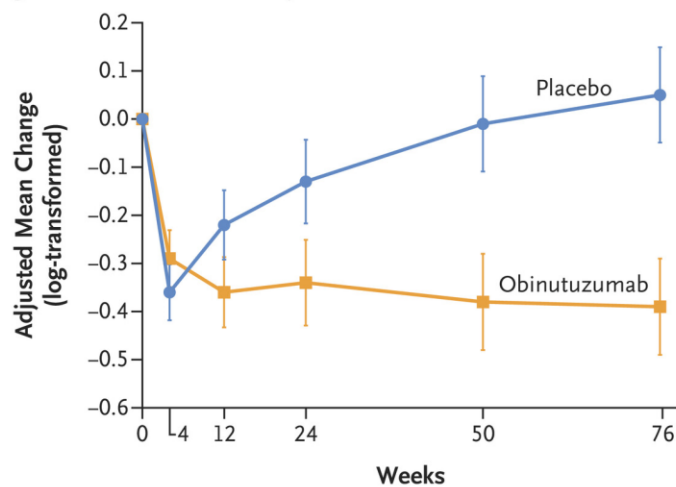
No. of Patients	271	271	271	271	271	271
No. with Missing Data	0	10	10	14	22	26

B Change in C4 Complement Level from Baseline



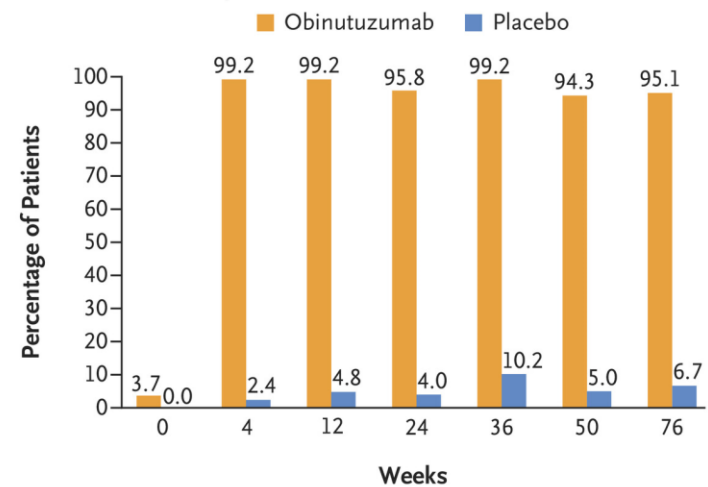
No. of Patients	271	271	271	271	271	271
No. with Missing Data	1	11	11	16	24	27

C Change in Anti-dsDNA Antibody Level from Baseline



No. of Patients	271	271	271	271	271	271
No. with Missing Data	0	7	10	22	27	27

D Patients with B-Cell Depletion over Time



No. of Patients	135	132	128	125	127	126	119	125	126	128	123	120	123	120
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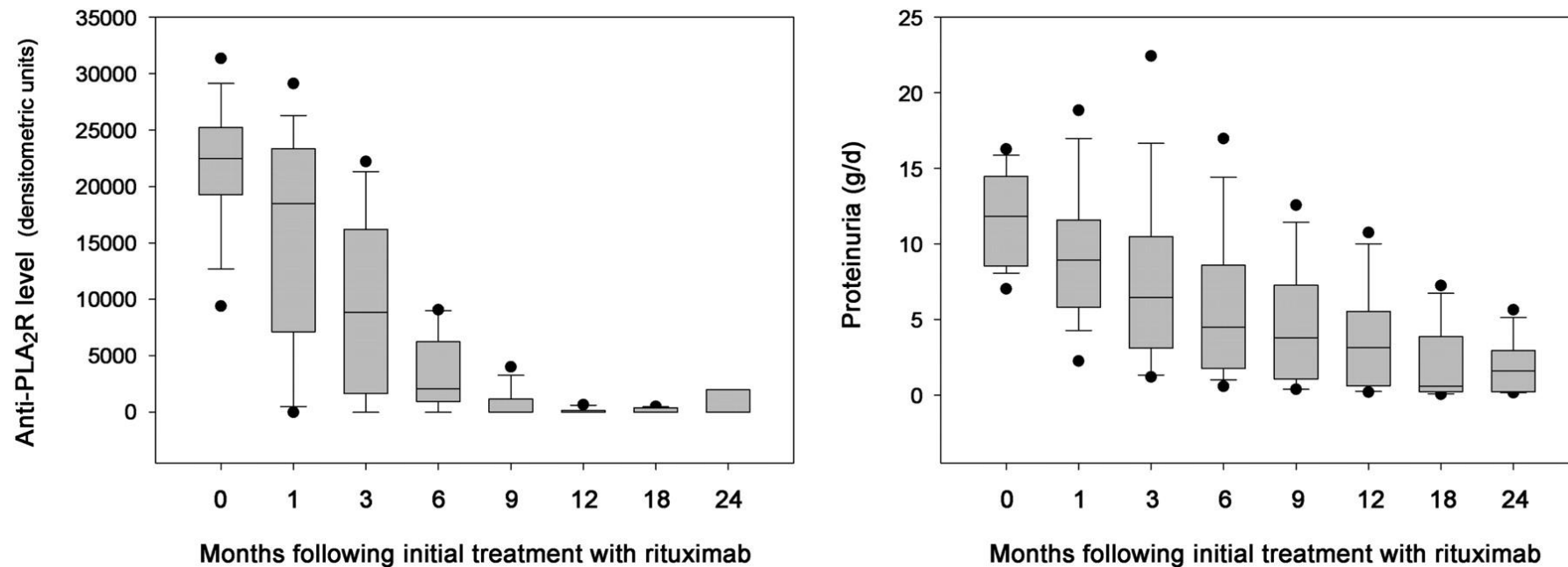
Rituximab-Induced Depletion of Anti-PLA₂R Autoantibodies Predicts Response in Membranous Nephropathy

Laurence H. Beck, Jr.,* Fernando C. Fervenza,[†]
David M. Beck,* Ramon G.B. Bonegio,* Fahim A. Malik,* Stephen B. Erickson,[†]
Fernando G. Cosio,[†] Daniel C. Cattran,[‡] and David J. Salant*

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JASN 22: 1543–1550, 2011

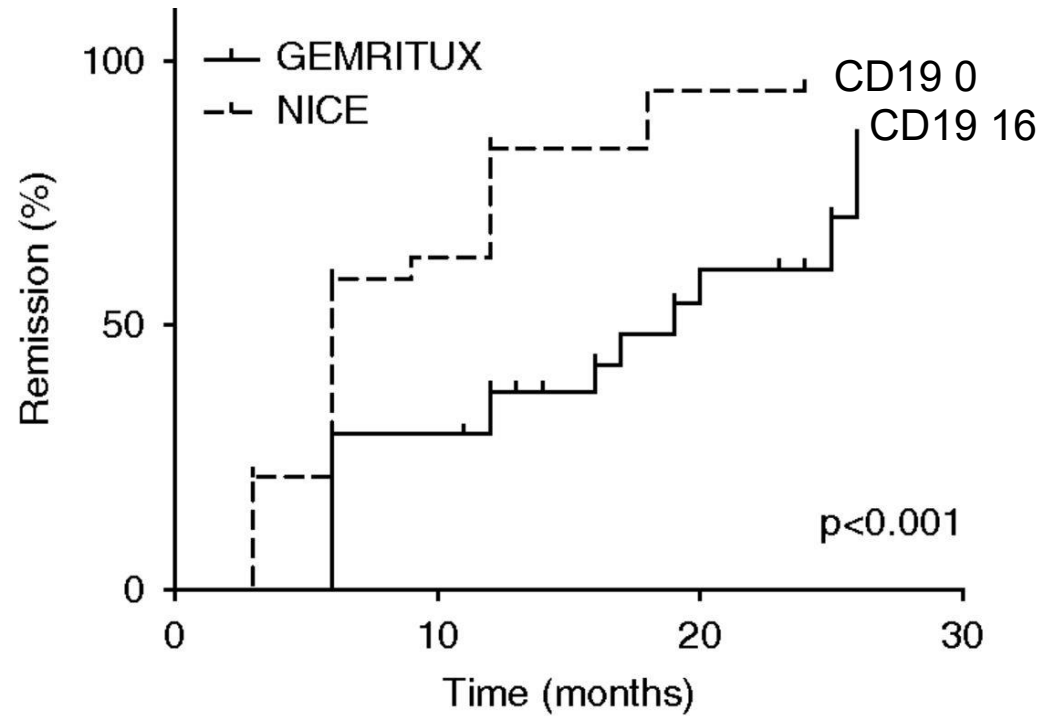


Anti-PLA₂R (left box plot) declines in advance of a more gradual decline of proteinuria (right) in those patients who cleared anti-PLA₂R. Boxes represent median (line) and 25th and 75th percentiles, with whiskers to the 10th and 90th percentiles. Outliers are represented by filled circles.

Adequate vs Inadequate CD19 Depletion in Membranous GN with Rituximab

Patient Characteristics	NICE Cohort (n=28)	GEMRITUX Cohort (n=27)
Baseline characteristics		
Age ^a	63 [51; 71]	51 [40; 63]
Sex ratio (F/M)	7/21	6/21
Body mass index (kg/m ²)	25.4 [23.3; 27.2]	25.4 [23.5; 28.4]
Proteinuria (g/g of creatinine)	5.9 [4.9; 7.6]	8.4 [4.4; 11.0]
Serum albumin (g/dl)	2.0 [1.5; 2.5]	2.1 [1.8; 2.6]
Dose of rituximab received (g) ^b	2 [2; 2]	1.45 [1.44; 1.46]
Serum creatinine (mg/dl)	1.2 [0.9; 1.5]	1.1 [0.9; 1.3]
BP (mm Hg)		
Systolic	121 [114; 130]	124 [110; 140]
Diastolic	82 [66; 80]	77 [64; 84]
Time from kidney biopsy to rituximab infusion	6.0 [6.0; 12.0]	8.0 [6.0; 13.0]
Anti-PLA2R1 titer (RU/ml) at first infusion	165.0 [67.0; 245.5]	102.5 [36.1; 672.5]
Spreading		
No	11 (39%)	7 (26%)
Yes	17 (61%)	20 (74%)
Characteristics at month 3		
Serum rituximab (μg/ml) ^b	3.3 [0.0; 10.8]	0.0 [0.0; 0.0]
Proteinuria (g/g of creatinine) ^b	2.6 [1.1; 5.0]	4.8 [3.2; 7.4]
Serum albumin (g/dl)	2.7 [2.0; 3.0]	2.7 [2.1; 3.1]
Anti-PLA2R1 (RU/ml) titer	0.0 [0.0; 19.0]	0.0 [0.0; 60.5]
Rate of PLA2R1 antibody depletion	16/27 (59%) ^c	14/25 (56%)
Spreading		
No	17 (61%)	13 (54%)
Yes	11 (39%)	11 (45%)
CD19 count (/mm ³) ^b	0.0 [0.0; 2.0]	16.5 [2.5; 31.0] ^d
Quantitative values are medians [interquartile ranges]; qualitative values are numbers. F/M, female/male; PLA2R1, M-type phospholipase A2 receptor.		
^a P<0.05.		
^b P<0.001.		
^c One point is missing.		
^d Two points are missing.		

Time To Remission

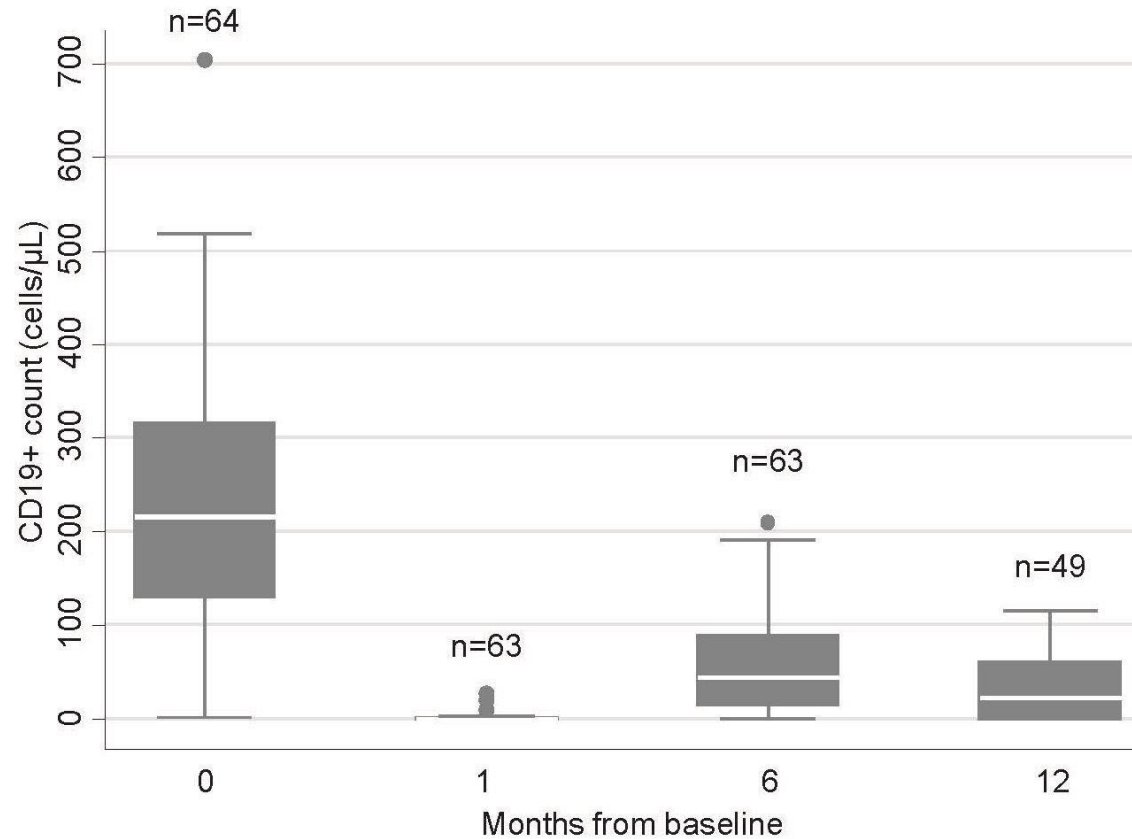


	M0	M6	M12	M18	M24	M30
NICE	28	12	6	4	4	4
GEMRITUX	27	19	17	15	13	11

CJASN 14: 1173–1182, 2019

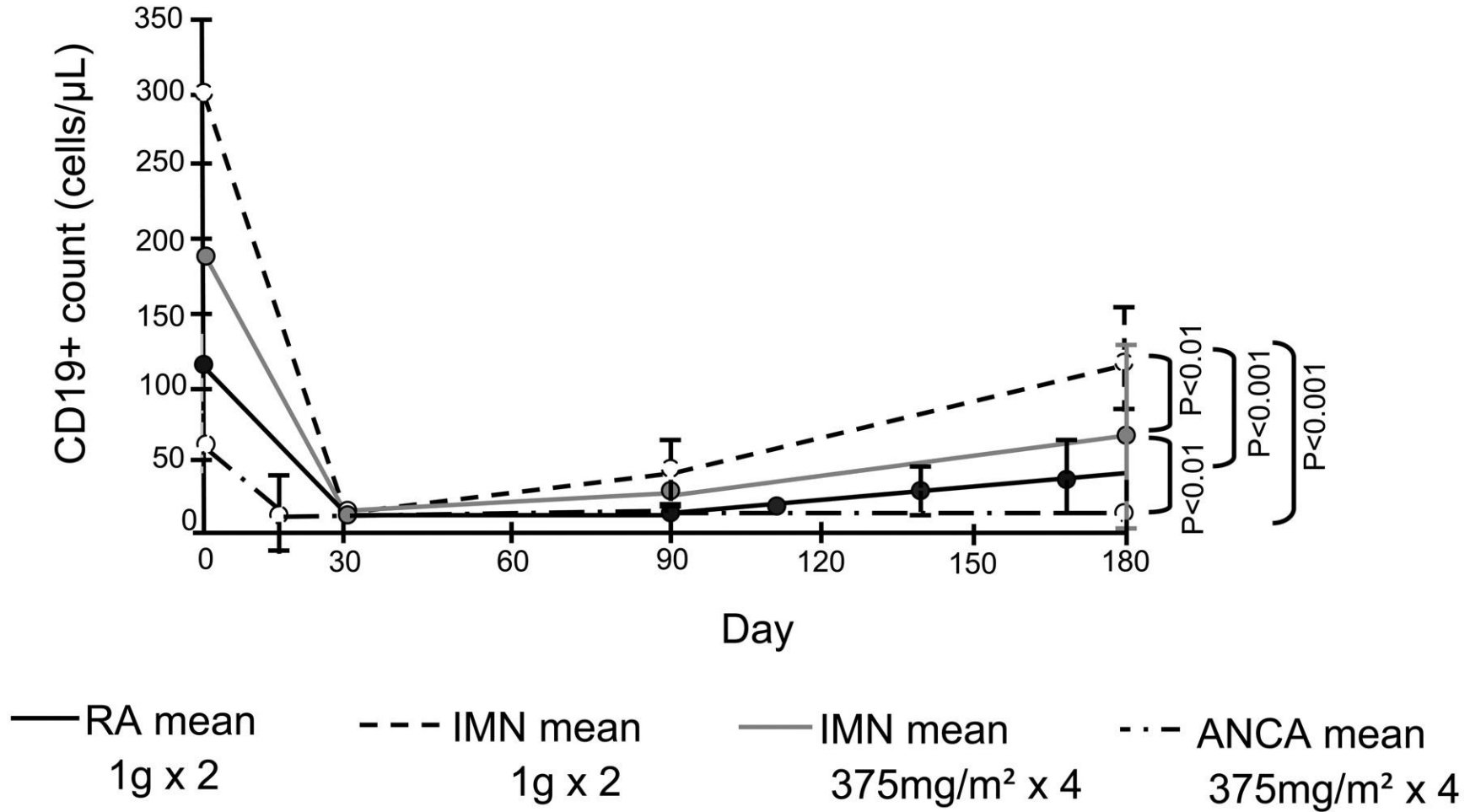


CD19 Depletion in the MENTOR Trial

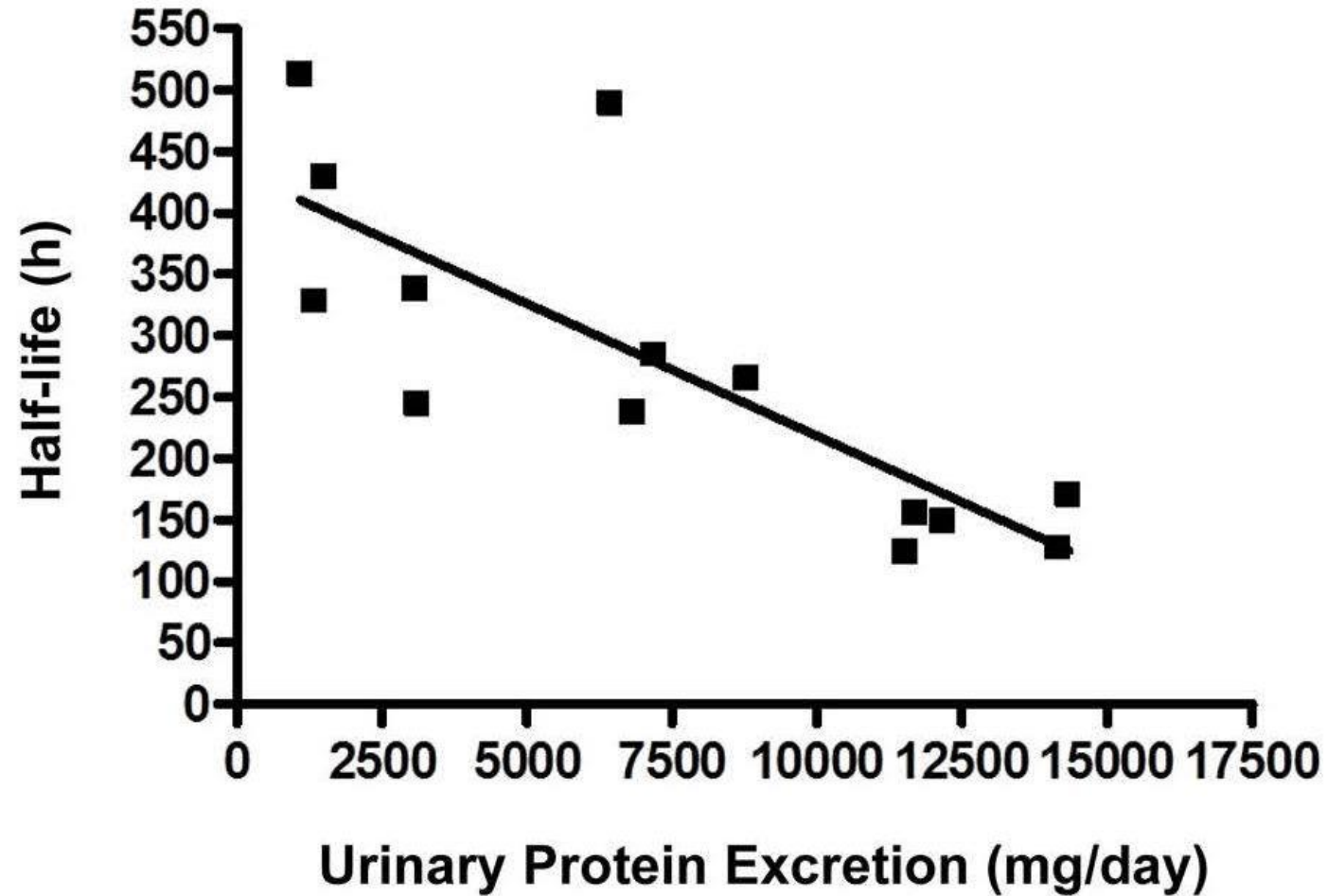


All patients randomized to rituximab with available data included for analysis of each time point; n, number of patients at each time point; Displayed are medians (white horizontal line), interquartile ranges (boxes), adjacent values (whiskers), and outliers (dots).

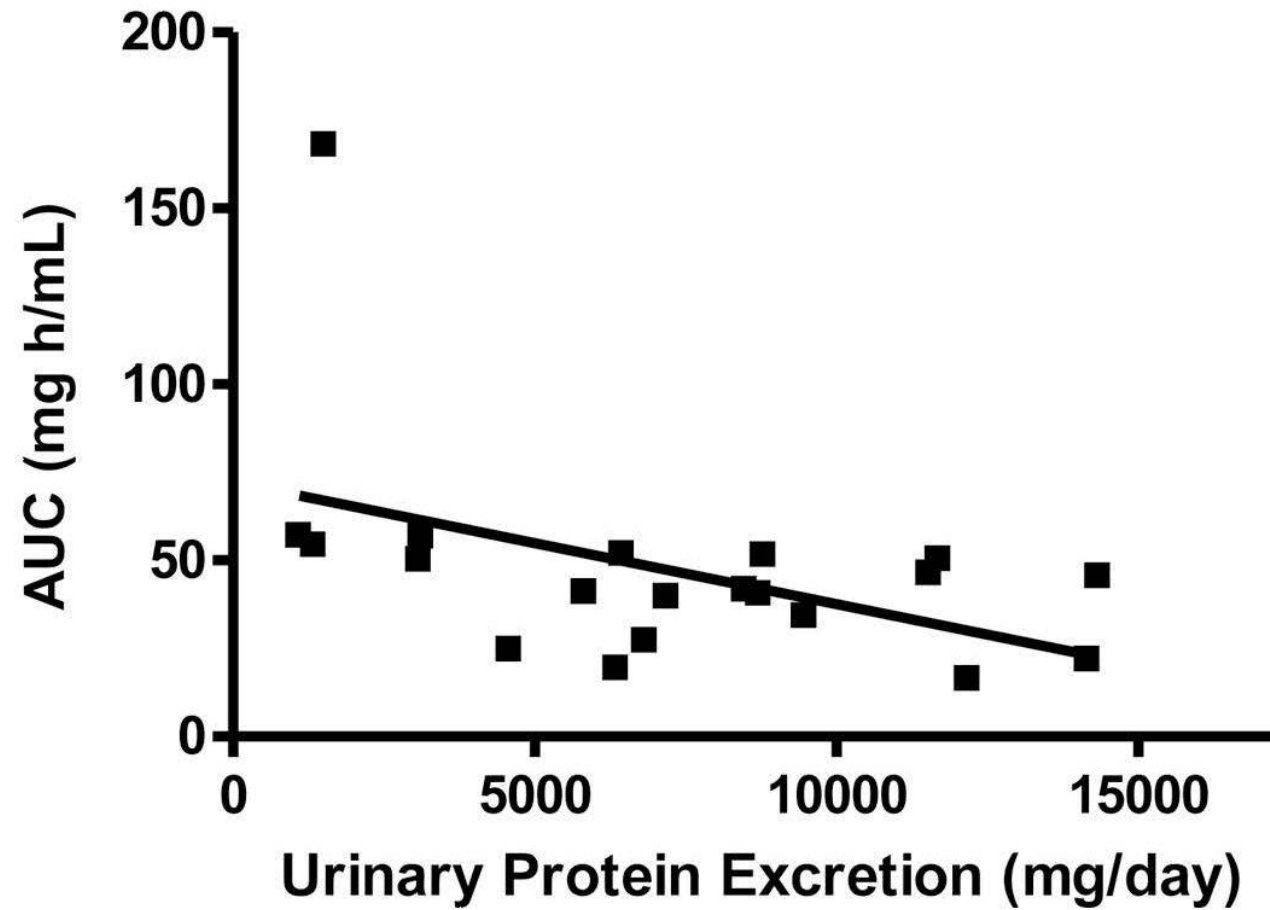
Dose-Finding for MENTOR



Altered Pharmacokinetics of Rituximab in Membranous GN



Altered Rituximab PK in Membranous GN



ORIGINAL ARTICLE

Obinutuzumab or Tacrolimus in Primary Membranous Nephropathy

Fernando C. Fervenza, M.D.,¹ Fan Fan Hou, M.D.,² Chuan-Ming Hao, M.D.,³
Gianna M. Kirsztajn, M.D.,⁴ Loreto Gesualdo, M.D.,⁵ Tomasz Hryszko, M.D.,⁶
Antonio Pisani, M.D.,⁷ Dario Roccatello, M.D.,^{8,9} Andrew S. Bomback, M.D.,¹⁰
Julie Rae, B.A.,¹¹ Farima Barmaki, M.D.,¹² Eriola Berisha, M.Sc.,¹³
Thomas Schindler, Ph.D.,¹² Theodore A. Omachi, M.D.,¹¹ Jay P. Garg, M.D.,¹¹
and Ana Malvar, M.D.,¹⁴ for the MAJESTY Trial Investigators*

N Engl J Med. 2026 Jun 5.



The MAJESTY Trial and its Implications

- A total of 142 patients underwent randomization. At week 104, complete remission was observed in 26 of 71 patients in the obinutuzumab group and in 4 of 70 patients in the tacrolimus group (37% vs. 6% with multiple imputation for missing data; adjusted difference, 31 percentage points; 95% CI, 18 to 44; $P < 0.001$). The analyses of complete or partial remission at week 104 and complete remission at week 76 also showed a significant treatment effect.
- Why tacro rather than rituximab? Would have required a much higher # of patients. Smaller studies suggest improved efficacy obi.
- FDA approval should be forthcoming for obinutuzumab – not available for rituximab.

Take Home Points

- Increasing options for treatment of both IgAN-associated nephron loss and IgAN-associated immunological “hits”.
- Reduction in galactose-deficient IgA versus treatment of downstream effects. Sequential strategy is evolving.
- Avacopan’s future in ANCA-associated vasculitis is in doubt.
- Obinutuzumab is now FDA-approved for SLE nephritis, with dramatic effects on serologies and renal outcome.
- Obinutuzumab is expected to be FDA-approved for membranous GN soon.