Targeting Drivers of IgAN Pathophysiology: Addressing Both Sides of the Coin

Meg Jardine

Disclosures – M Jardine

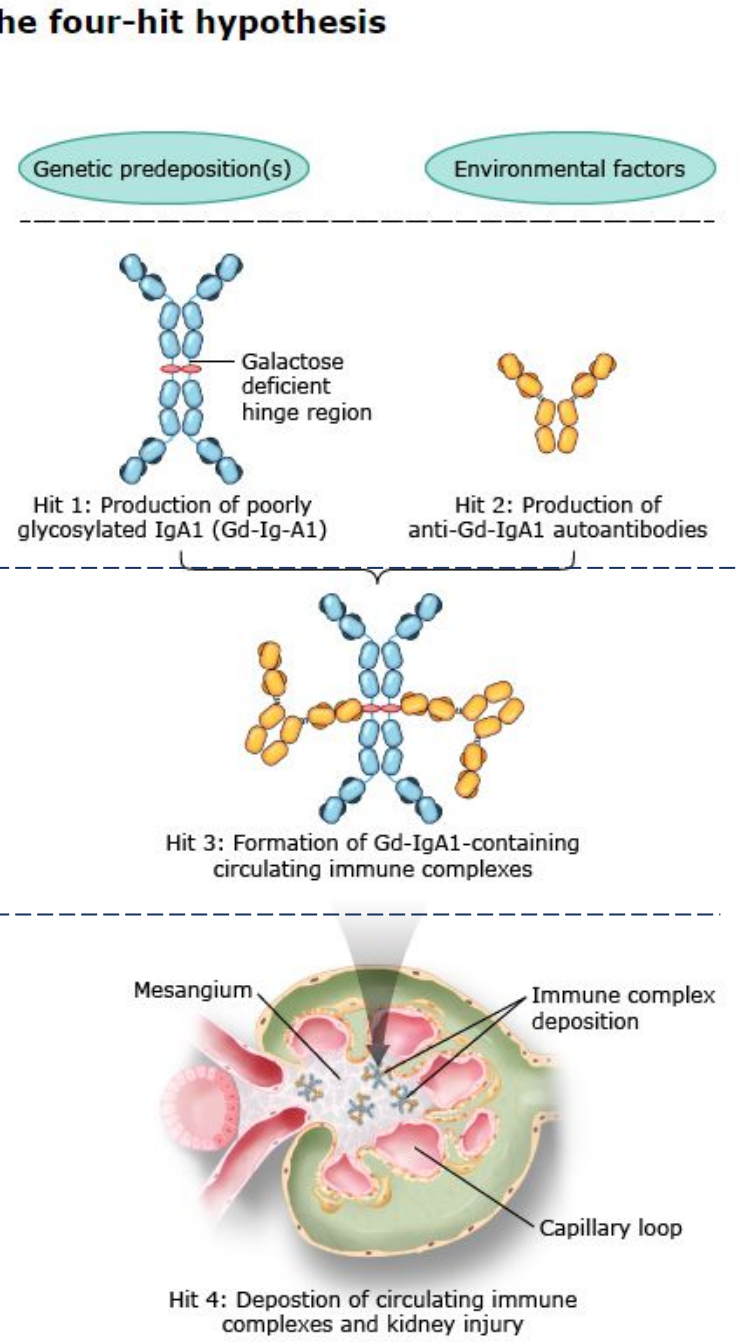
- Supported by Australian Government NHMRC Investigator Grant
- Responsible for research projects that have received funding from Amgen, Boehringer Ingelheim, CSL, Dimerix, Eli Lilly, Gambro, MSD and Vantive
- Have received fees for Advisory, Steering Committee and/or Scientific Presentations from Akebia, Amgen, Astra Zeneca, Baxter, Bayer, Boehringer Ingelheim, Cesas Medical, Chinook, CSL, Janssen, Medscape, MSD, Novatis, Novo Nordisk, Occuryx, Roche and Vifor
- All consultancy, honoraria or travel support directed to my institution

Contents

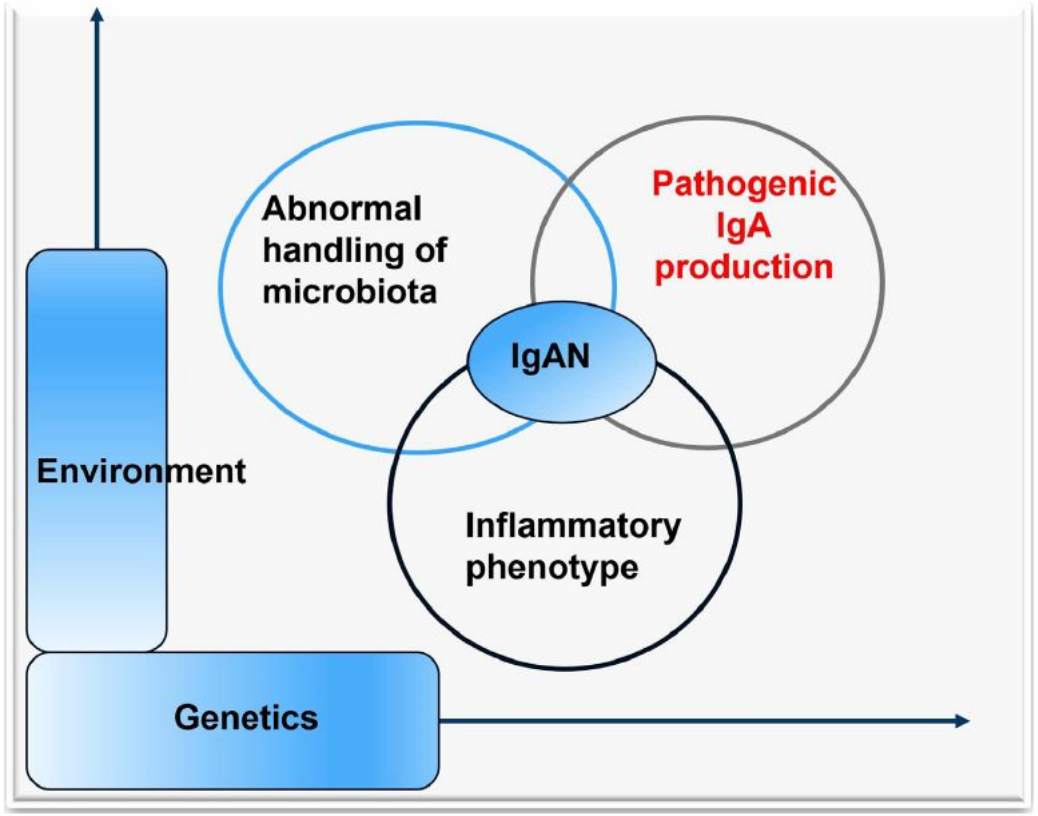
- The 4 hit hypothesis for IgAN pathophysiology
- Emerging treatments
  - ERAs
  - B-cell therapies
  - Anti-complement therapeutics
  - Possibly other agents under investigation (eg finerenone, aldosterone synthase inhibitors)

The IgAN four-hit hypothesis

Hit 1	Increase in galactose-deficient-IgA1 (Gd-IgA1) in the circulation believed to be derived from a mucosal source
Hit 2	Autoantibodies formed to Gd-IgA1
Hit 3	Immune complexes form
Hit 4	Immune complexes deposit in kidney mesangium – cascade of mesangial cell proliferation, cytokine release, complement activation, podocyte injury, etc.. Final common pathway of kidney injury and fibrosis



Complex interactions of genetic risk loci with environmental exposures in IgAN



IgAN is thought to occur when individuals with genetic susceptibility traits come into contact with disease-triggering environmental risk factors such as infections, resulting in the activation of both innate and adaptive immunity

X Zhou, H Zhang *SeminNephrol* 44:151567 2025

ERAs

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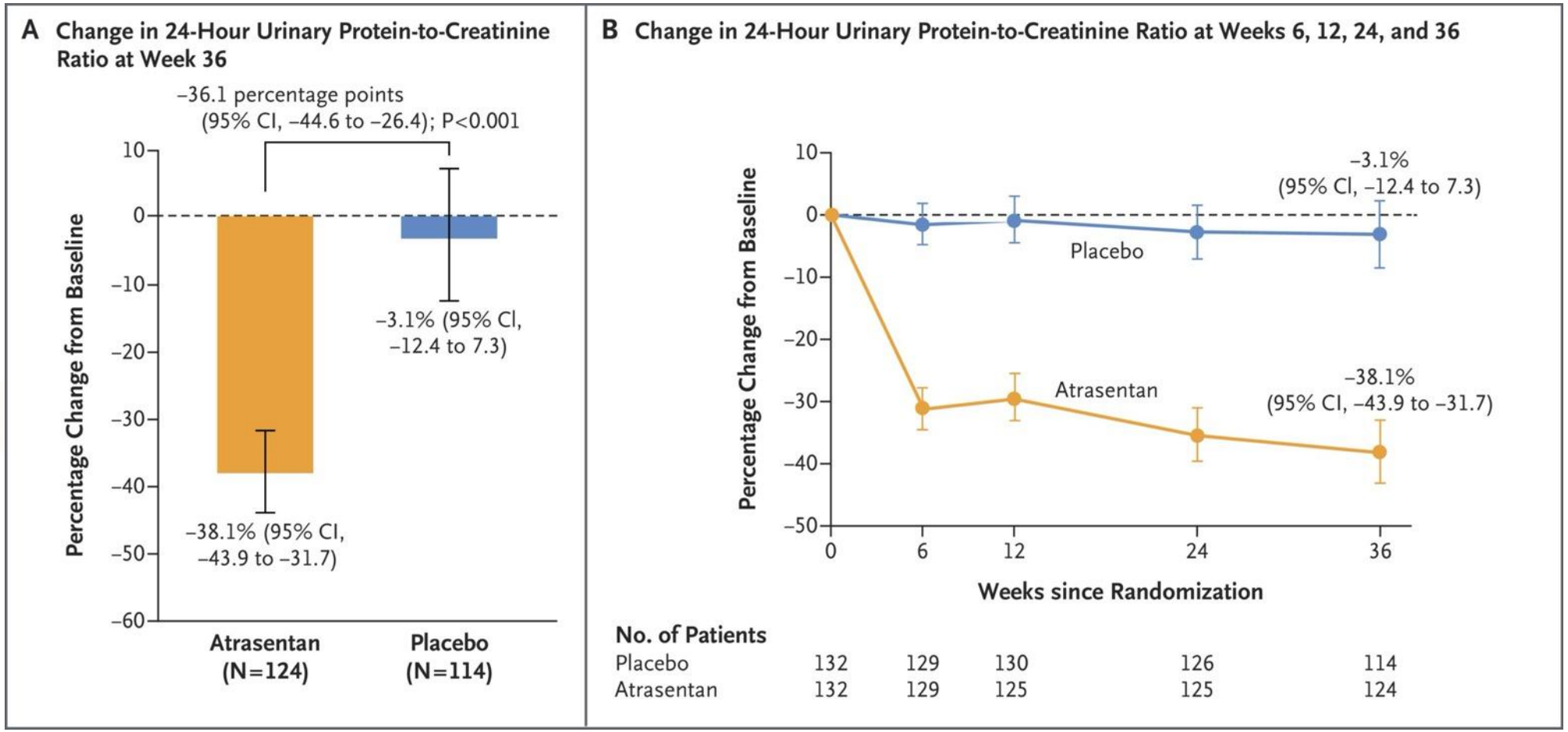
ERAs: Atrasantan reduces proteinuria in IgAN

−36.1% (−44.6, −26.4), p<0.0001



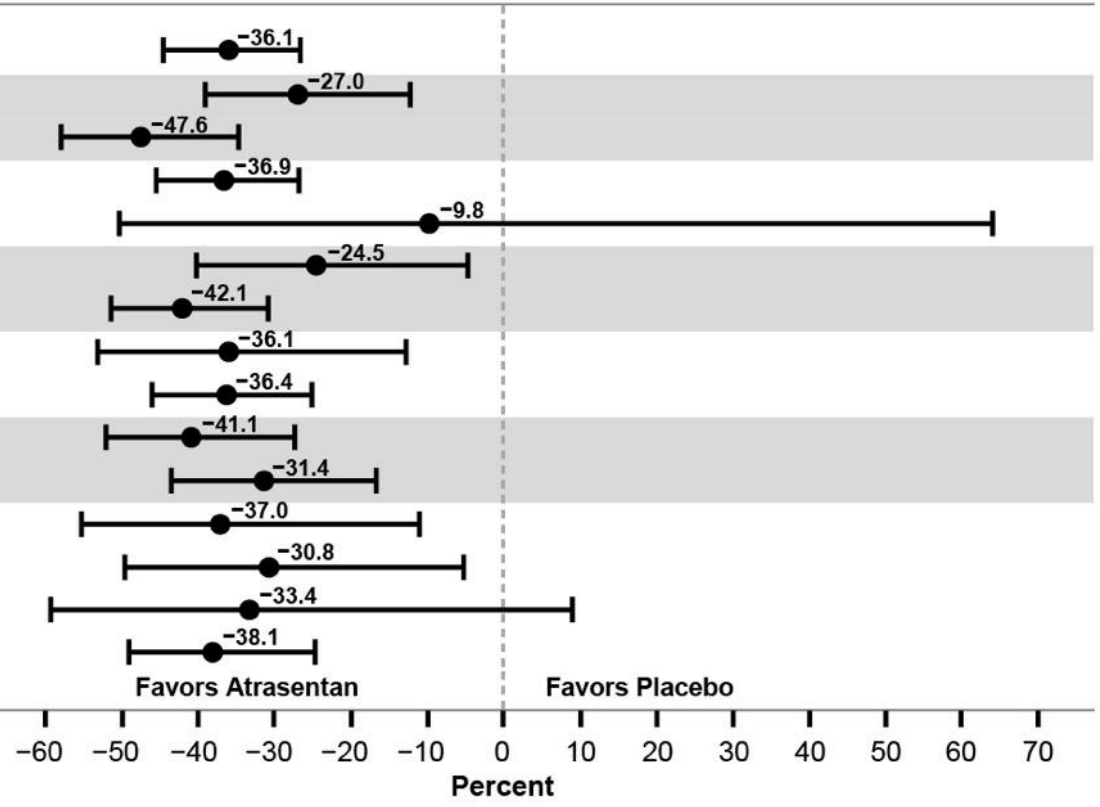
ALIGN

Change in 24-Hour Urinary Protein-to-Creatinine Ratio (Primary Outcome).

HJL Heerspink *NEJM* 2025 392(6):544-554

Atrasentan effect was consistent across prespecified subgroups -1/2

Subgroup		Atrasentan n (N=135)	Placebo n (N=135)
Overall		132	132
Gender	Male	80	76
	Female	52	56
Age	< 65 years	121	126
	≥ 65 years	11	6
Race	White	49	47
	Other	83	85
Ethnicity	Hispanic or Latino	31	24
	Not Hispanic or Latino	96	107
Region	Asia	62	61
	Non-Asia	70	71
Region	North America	20	26
	Latin America	29	23
	Europe	10	12
	Asia-Pacific	73	71

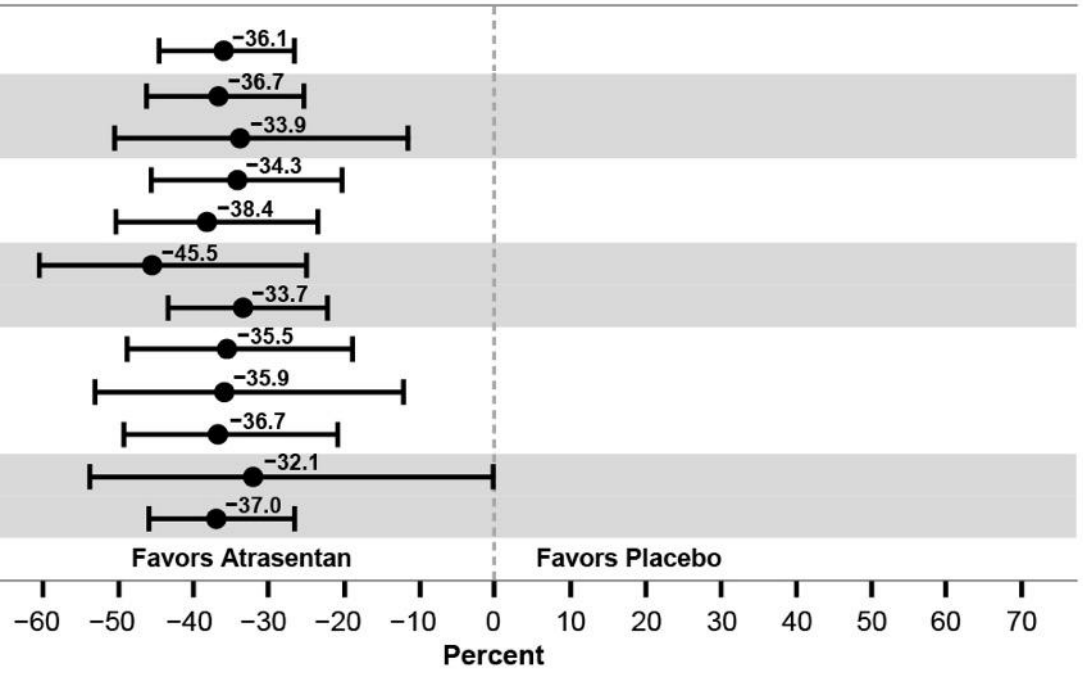


– UPCR based on 24-hour urine collection. Based on MMRM models and subgroup analysis of UPCR methods. Separate MMRM model fit for each subgroup variable. UPCR values censored for intercurrent events (i.e., restricted medication use, chronic dialysis, kidney transplant) beginning at start date of earliest event. LSMeans: Least-square means

HJL Heerspink *NEJM* 2025 392(6):544-554

Atrasentan effect was consistent across prespecified subgroups -2/2

Subgroup		Atrasentan n (N=135)	Placebo n (N=135)	Difference in LS Means and 95% CI
Overall		132	132	−36.1
Screening UPCR	< 2000 mg/g	100	100	−36.7
	≥ 2000 mg/g	32	32	−33.9
Baseline UPCR	< 1500 mg/g	70	75	−34.3
	≥ 1500 mg/g	62	57	−38.4
Blood Pressure	SBP ≥ 140 or DBP ≥ 90 mmHg	27	27	−45.5
	SBP < 140 and DBP < 90 mmHg	105	105	−33.7
eGFR	≤ 45 mL/min/1.73m^2	53	51	−35.5
	> 45 − ≤ 60 mL/min/1.73m^2	25	28	−35.9
	> 60 mL/min/1.73m^2	54	53	−36.7
Diuretic Use	Yes	21	16	−32.1
	No	111	116	−37.0

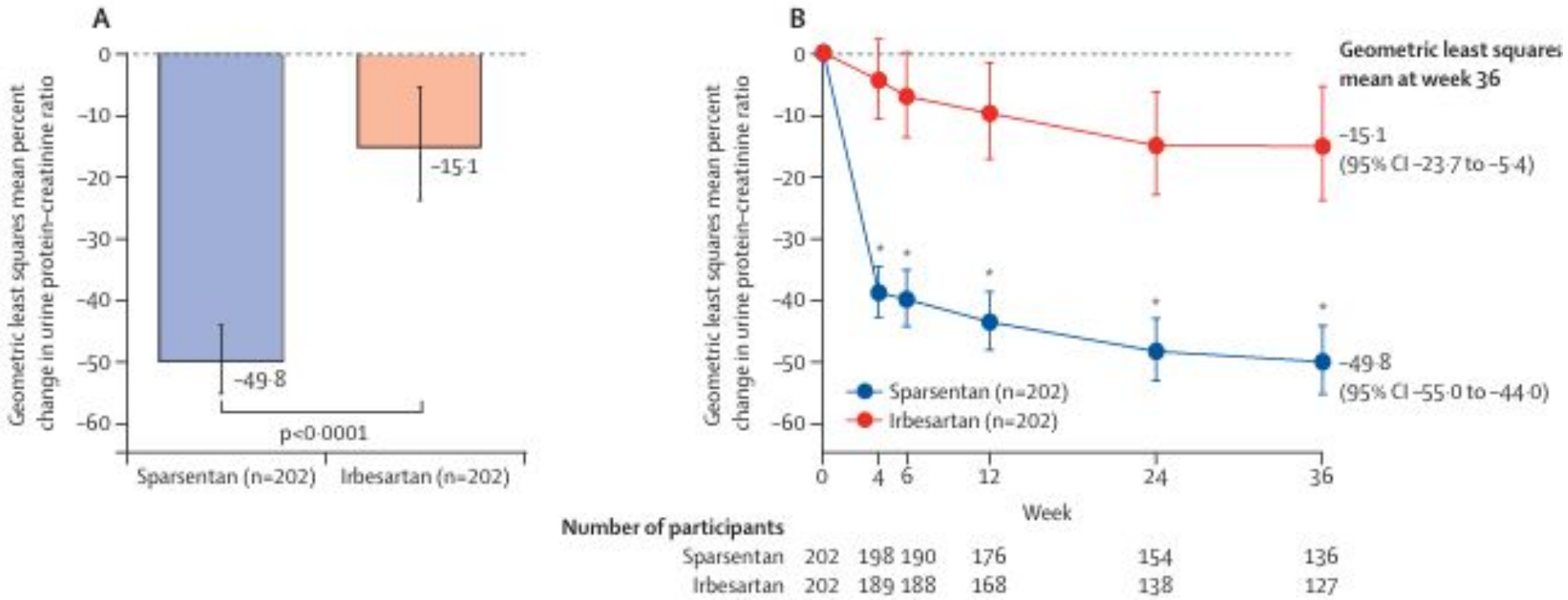


UPCR based on 24-hour urine collection. Based on MMRM models and subgroup analysis of UPCR methods. Separate MMRM model fit for each subgroup variable. UPCR values censored for intercurrent events (i.e., restricted medication use, chronic dialysis, kidney transplant) beginning at start date of earliest event. LSMeans: Least-square means

HJL Heerspink *NEJM* 2025 392(6):544-554

Sparsentan reduces proteinuria in IgAN

PROTECT



HJ Heerspink Lancet 2023; 401: 1584–94

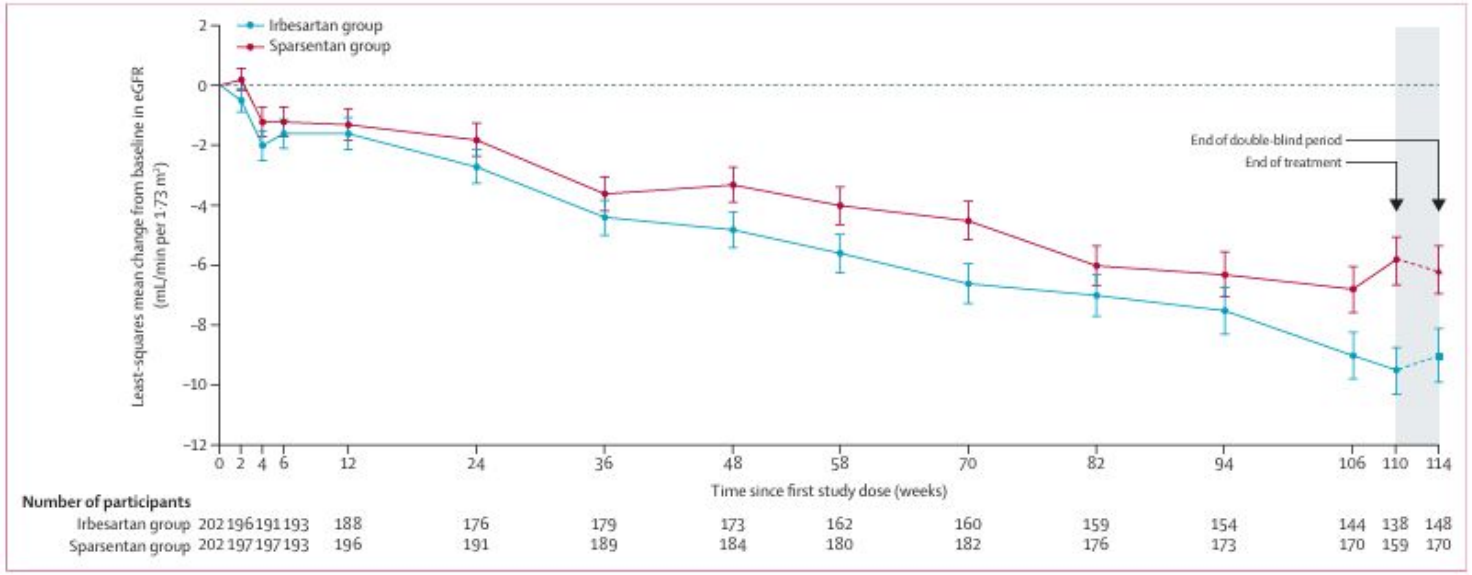
Sparsentan eGFR endpoints at 2 years

PROTECT

	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	−2·7 (−3·4 to −2·1)	−3·8 (−4·6 to −3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	−2·9 (−3·6 to −2·2)	−3·9 (−4·6 to −3·1)	1·0 (−0·03 to 1·94)	0·058
Other secondary efficacy endpoint*				
Absolute change from baseline to week 110, mL/min per 1·73 m²	−5·8 (−7·4 to −4·2)	−9·5 (−11·2 to −7·9)	3·7 (1·5 to 6·0)	..
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	−6·1 (−7·7 to −4·5)	−9·0 (−10·7 to −7·2)	2·9 (0·5 to 5·3)	..

Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

p= 0.037
p= 0.058



Rovin *Lancet* 2023; 402: 2077–90

B-cell targetting

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B cell targeting

Treatments targeting GdIgA1 positive presenting cells

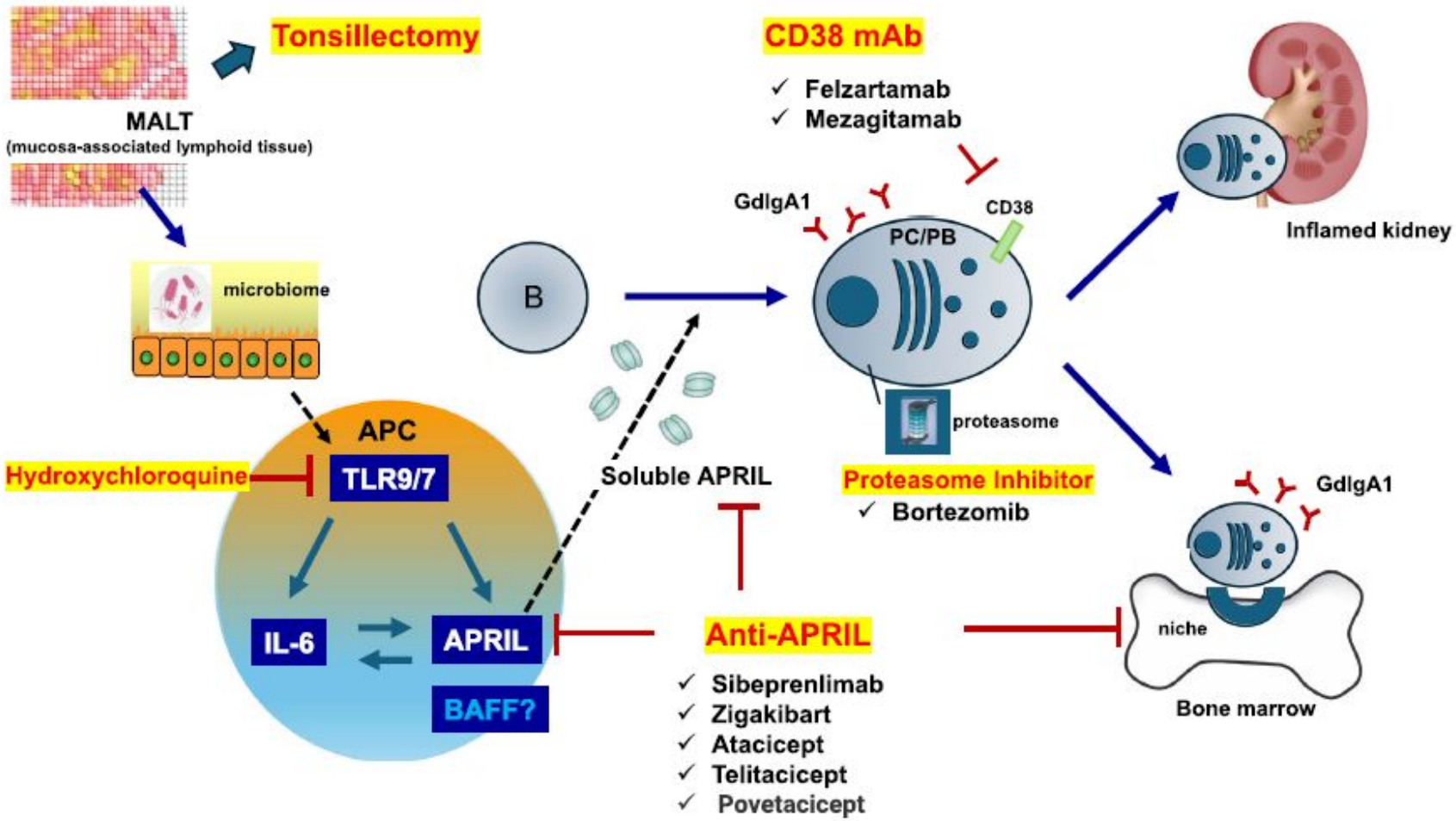


FIGURE 1 Treatment targeting GdIgA1$^+$ PC. APC, antigen-presenting cells; APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; GdIgA1, galactose-deficient IgA1; mAb, monoclonal antibody; MALT, mucosa-associated lymphoid tissues; P1/2/3, phase 1/2/3 clinical studies PC/PB, plasma cell/plasma blast; TLR, toll-like receptor.

Suzuki *Nephrology*. 2024;29(Suppl. 2):39–43.

Pathogenesis based clinical trials in IgA nephropathy

Modulate B cell activation
Inhibitors of BAFF/APRIL

Complement modulation
Inhibit AP/LP/TP

Non-immunosuppressive
ET_AR inhibitor
SGLT2 inhibitor
MRA

Agent (company)	Trial phase	Therapeutic class (route)	NCT#	Publish (PMID)
Rituximab (Roche, Switzerland)	4	Immunomodulator-CD19 inhibitor (IV)	00498368	26032537
Felzartamab (HI-Bio, America)	2	Immunomodulator-CD38 inhibitor (SC)	05065970	/
Mezagitamab (Takeda, Japan)	1	Immunomodulator-CD38 inhibitor (SC)	05174221	/
Telitacicept (RemeGen, China)	2	Immunomodulator-blys/APRIL inhibitor (SC)	04291781	36938094
Atacicept (Serono/Merck) inhibitor	2	Immunomodulator-blys/APRIL inhibitor (SC)	02808429	35967104
BION-1301 (AduroBiochem)	1	Immunomodulator-APRIL inhibitor (IV)	03945318	/
VIS-649(Visterra)	2	Immunomodulator-APRIL inhibitor (IV)	04287985	/
ADR-101(RhotoPharm,Japan)	1	Immunomodulator-mesenchymal stem cells (IV)	04342325	35692547
LNP-023-iptacopan(Novartis)	3	Complement inhibitor-factor B inhibitor (APPLAUSE-IgAN) (oral)	04578834	37180505
FB-LRx(IONIS)	2	Complement inhibitor-anti-sense factor B inhibitor (SC)	04014335	/
OMS-721-narsoplimab(Omeros)	3	Complement Inhibitor-MASP inhibitor (ARTEMIS-IgAN) (IV)	03608033	/
ALN-CC5-Cemdisarin(Alnylam)	2	Complement Inhibitor-C5 inhibitor (SC)	03841448	/
CCX-168-avacopan(Chemocentryx)	2	Complement inhibitor-C5a receptor inhibitor (oral)	02384317	/
Ravulizumab(Alexion/Astra-Zeneca)	2	Complement inhibitor-C5 inhibitor (IV)	04564339	/
APL-2(Apellis)	2	Complement inhibitor C3b inhibitor (SC)	03453619	/
BCX9930 (BioCryst Pharmaceuticals)	2	Complement inhibitor-factor D inhibitor (oral)	05162066(	/
ALXN2050 (Alexion)	2	Complement inhibitor-factor D inhibitor (oral)	05097989	/
KP104 (Kira Pharmacenticals, America)	2	Complement inhibitor CFH and C5 inhibitor (SC)	05517980	/
CHK-01-atresentan(Chinook)	3/2	Endothelin A receptor inhibitor (oral)	04573478 04573920	/
Sparsentan(Travere/Retrophin)	3	Combined endothelin A/angiotensin II receptor inhibitor-PROTECT (oral)	03762850	37015244
RTA-402-bardoxolonemethyl(Reata)	2	Nuclear factor erythroid-derived 2-related factor 2 agonist–PHOENIX (oral)	03366337	/

https://clinicaltrials.gov/ct2/home

APRIL inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

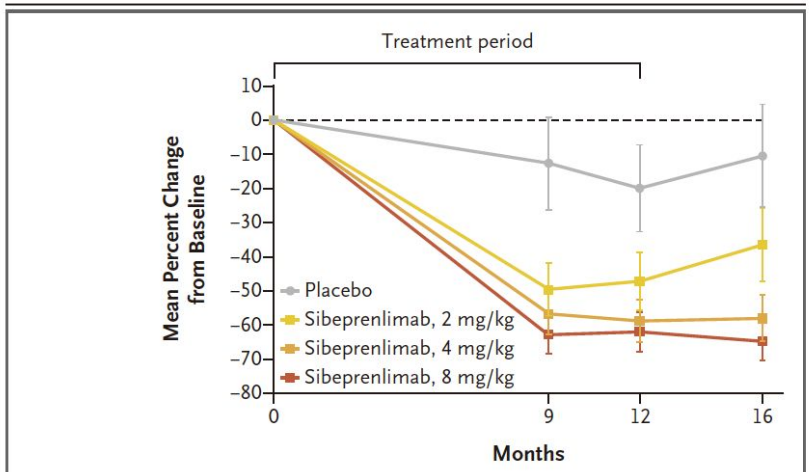
ORIGINAL ARTICLE

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

Mohit Mathur, M.D., Jonathan Barratt, Ph.D., Bobby Chacko, M.D., D.M., Tak Mao Chan, M.D., D.Sc., Laura Kooienga, M.D., Kook-Hwan Oh, M.D., Ph.D., Manisha Sahay, M.D., Yusuke Suzuki, M.D., Ph.D., Muh Geot Wong, M.B., B.S., Ph.D., Jill Yarbrough, B.A., Jing Xia, Ph.D., and Brian J.G. Pereira, M.D., for the ENVISION Trial Investigators Group*

In 155 patients with IgAN, 12 months of sibeprenlimab treatment resulted in significant reduction in proteinuria, stabilization of eGFR decline, and robust suppression of serum APRIL, as well as serum Gd-IgA$_1$, compared to placebo

The efficacy and safety data of the 4 mg/kg dosing noted in phase 2 is very encouraging for the phase 3 prospect as this was the dose chosen for the VISIONARY trial.



No. of Patients				
Placebo	38	35	35	35
Sibeprenlimab, 2 mg/kg	38	35	35	35
Sibeprenlimab, 4 mg/kg	41	40	38	38
Sibeprenlimab, 8 mg/kg	38	36	37	37

Figure 1. Change from Baseline over Time in the 24-Hour Urinary Protein-to-Creatinine Ratio.

This analysis was performed with the use of a mixed model for repeated measures in the modified intention-to-treat population. The mean percent change is calculated as (1−exponentiated least-squares mean) × 100%. I bars indicate standard errors.

MATHUR, M. ET AL. N ENGL J MED 2024; 390:20-31.

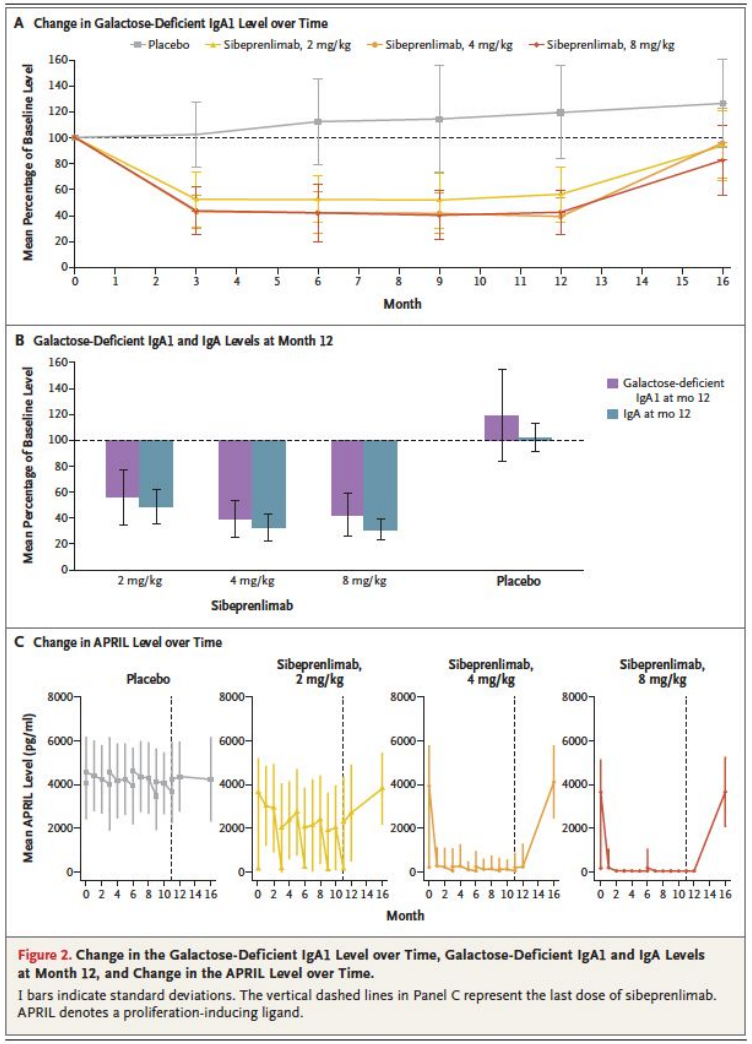


Figure 2. Change in the Galactose-Deficient IgA1 Level over Time, Galactose-Deficient IgA1 and IgA Levels at Month 12, and Change in the APRIL Level over Time.

I bars indicate standard deviations. The vertical dashed lines in Panel C represent the last dose of sibeprenlimab. APRIL denotes a proliferation-inducing ligand.

Sibeprenlimab was generally safe and well tolerated, without evidence of undesirable toxicity or clinically meaningful immunosuppression

A Phase 3 trial is underway to investigate the efficacy and safety of sibeprenlimab in a larger population of patients with IgAN (NCT05248646; the Visionary study)

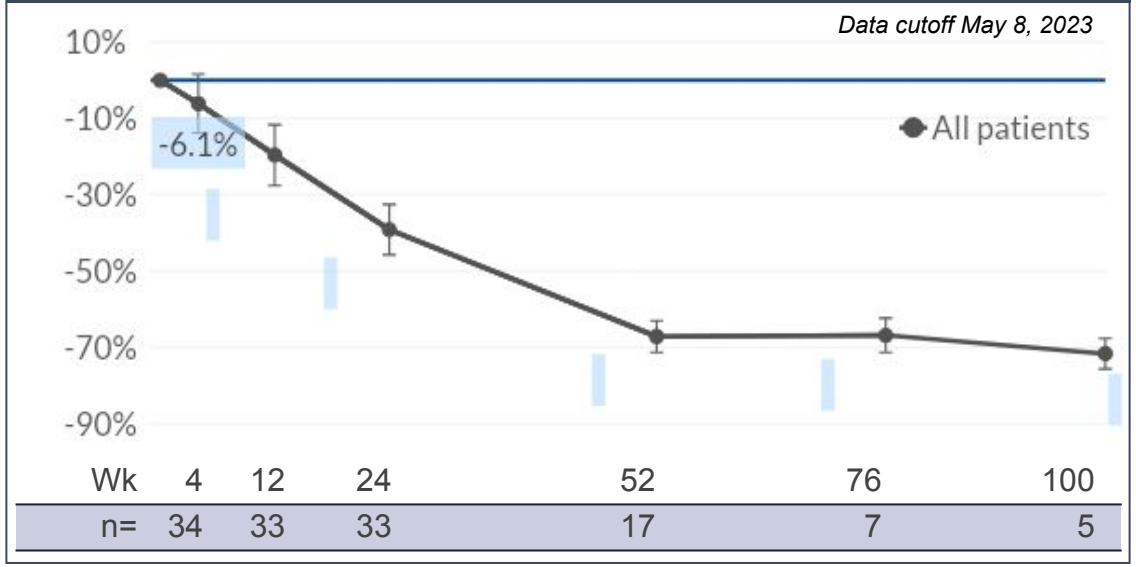
APRIL inhibitor

Zigakibart - humanized IGg4 monoclonal antibody blocks APRIL binding to receptors

Zigakibart treatment results in sustained, clinically meaningful proteinuria reduction in patients with IgAN

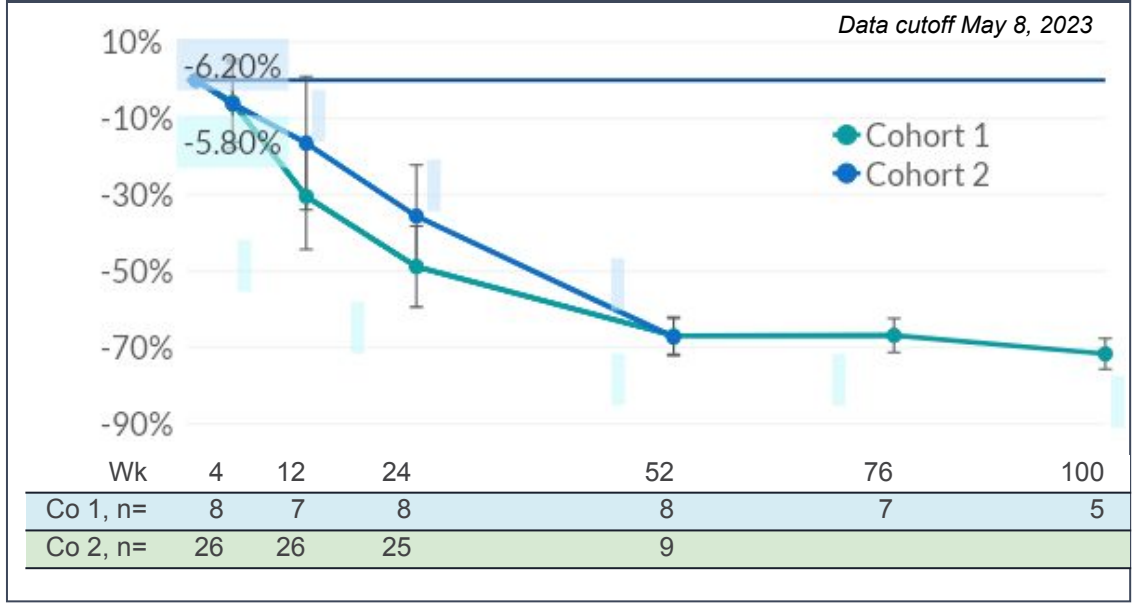
- Reductions in UPCR were seen by Week 12 in patients with IgAN across a wide range of baseline proteinuria levels
- UPCR continued to decline through 1 year in both cohorts, and this decline was maintained through 2 years in Cohort 1, providing evidence of sustained efficacy

UPCR, Combined Cohorts
% Reduction (Geometric Mean ± SE)



Median (range) baseline protein excretion: 1.1 (0.3, 7.0) g/day

UPCR, Cohort 1 and Cohort 2
% Reduction (Geometric Mean ± SE)



Median (range) baseline protein excretion:
Cohort 1, 1.2 (0.7, 6.5) g/day; Cohort 2, 1.0 (0.3, 7.0) g/day

Clinical trials targeting B-cells in IGAN

Trial Name	VISIONARY	Telitacicept	ORIGIN	BION-1301	Povitacicept
Product and MOA	Sibeprenlimab (APRIL inhibitor)	Telitacicept (BAFF and APRIL inhibitor)	Atacicept (dual BAFF and APRIL inhibitor)	BION-1301 (APRIL inhibitor)	Anti-APRIL and BAFF inhibitor)
Sponsor	Otuska	China only	Vera therapeutic	Novartis	Vertex
Trial designs	Double blind	Double blind	Double blind	Pooled data from phase 1/2 (double blind)	Double blind
Age (years)	≥18	≥18	≥18	≥18	≥18
Biopsy-proven IgA	Yes	Yes	Yes (<10 years)	Yes (<10 years)	Yes
Included HSP/IgA vasculitis	Yes	No	No	No	No
Proteinuria (g/day)	>0.75 (24 h) or >1g/g	>0.75	>0.75 and ≤ 5	≥0.5 (24 h) or ≥0.5 (uPCR)	≥ 0.75 (uPCR) or ≥ 1.0 (24 h)
eGFR ($mL/min/1.73m^2$)	>30 but <90 Exploratory cohort	>35	≥ 30	>30	≥30
Duration of RAASi (months)	3	Stable dose duration not specified	3	3	3
Route of administration and frequency	S/C monthly	Subcutaneous weekly, 160 mg, 240 mg	Subcutaneous weekly, 25 mg, 75 mg, 150mg	Multiple doses Intravenous or subcutaneous	S/C Monthly
Primary outcomes	Change in proteinuria at 9 months and eGFR slope in 2 yrs	Change in proteinuria at 24 weeks	Safety and tolerability (% with treatment-emergent AE)	Safety and tolerability (% with treatment-emergent AE)	Safety Change in proteinuria at 12 months

Complement inhibition development

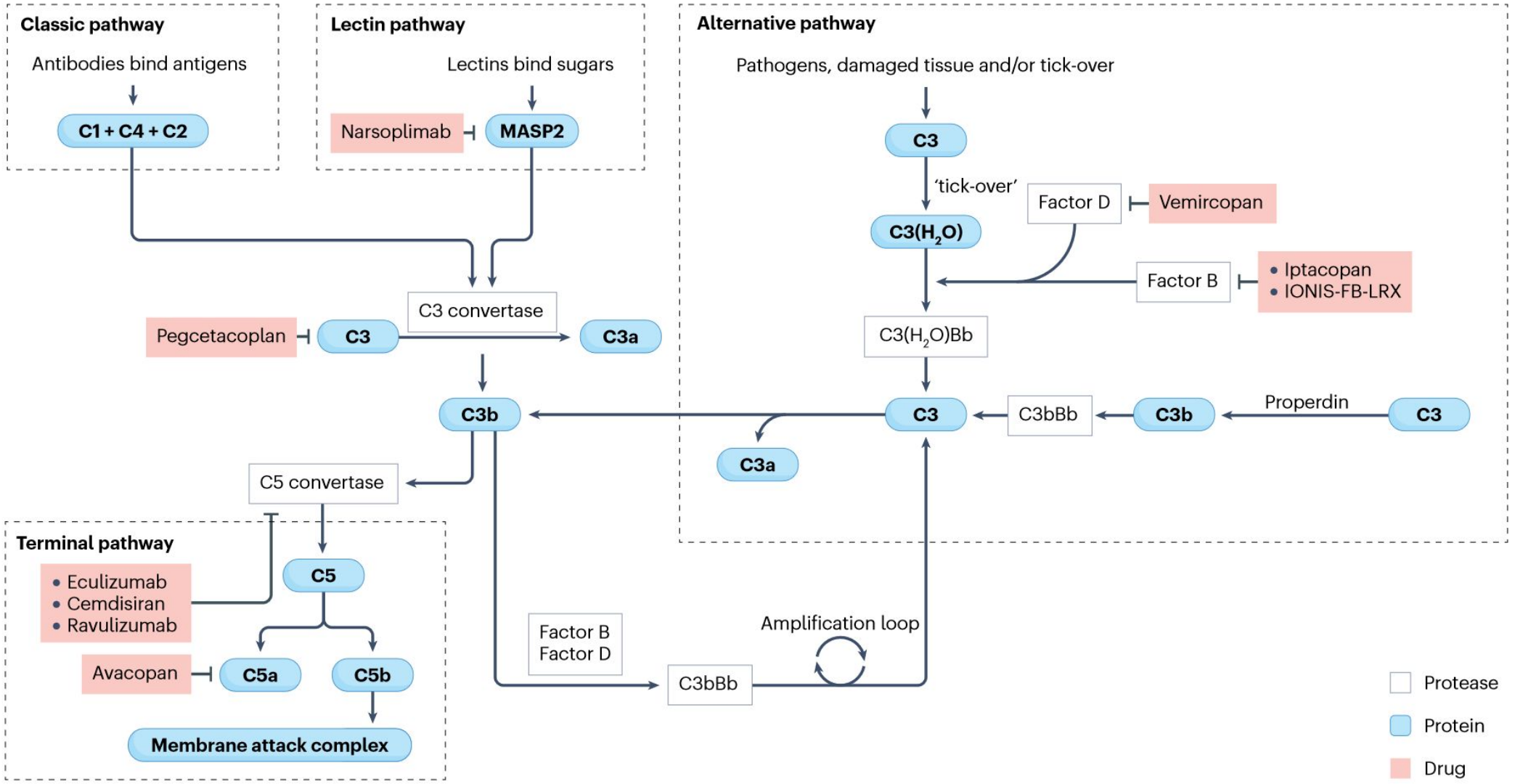
TABLE 6 Complement inhibition in IgAN.

Target	Agent	Administration	Published trials	Results	Comment	Pending trials
Factor B	Iptacopan	Oral	Zhang/ 2024 (168)	24% Reduction in 24-h urine P/C ratio at 3 months	Further decrease in proteinuria at 6 months Appears safe Phase 3 trial awaited	NCT04557462 NCT04578834
	IONIS-FB-L_{RX}	Subcutaneous	NA	NA	NA	NCT04014335
Factor D	Vermircopan	Oral	NA	NA	NA	NCT05097989
	Pelecopan	Oral	NA	NA	NA	NCT05162066
MASP-2	Narsoplimab	Intravenous	Lafayette/ 2020 (169)	54%–95% Reduction of 24-h UPE at 18 weeks in patients on tapering steroids No benefit in RCT of steroid naïve at 18 weeks	Phase 3 trial terminated by sponsor for lack of efficacy	NCT02682407
C3	Pegcetacoplan	Subcutaneous	Dixon/ 2023 (170)	1.1% Reduction in 24-h urine P/C ratio at 48 weeks	Only 6 IgAN patients Included Ce glomerulopathy and lupus patients	NA
C5	Cemdisiran	Subcutaneous	Barratt/ 2024 (171)	37.4% Reduction in 24-h urine P/C ratio at 32 weeks 98.7% reduction in serum C5 at 32 weeks	Well-tolerated Phase 2	NA
	Ravulizumab	Intravenous	NA	NA	NA	NCT06291376
C5 receptor	Avacopan	Oral	Bruchfeld/ 2022 (172)	6 of 7 Patients had improve slope of urine P/C ratio	Small and uncontrolled	NA

MASP-2, mannan-binding lectin associated serine protease-2; NA, not available; P/C, protein/creatinine; UPE, urine protein excretion.

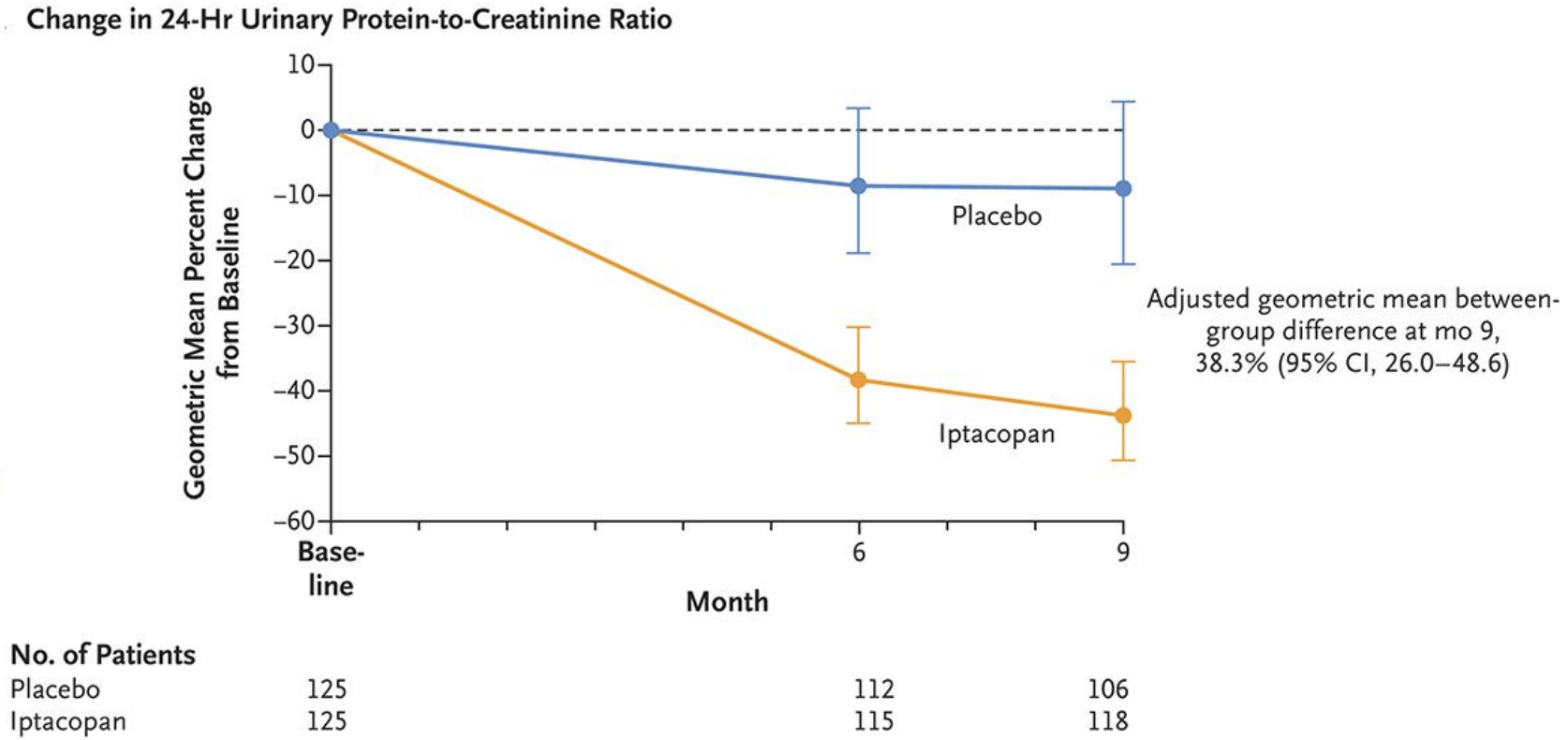
Filippone EJ *Front. Immunol*. 2024 15:1436923 doi: 10.3389/fimmu.2024.1436923

Targeting complement system in IGAN



Stamellou E, Seikrit C, Tang SCW, et al. IgA nephropathy. Nat Rev Dis Primers. 2023;9(1):67.

Iptacopan reduces proteinuria in IgA



APPLAUSE IgAN

Iptacopan inhibits alternative complement pathway through binding factor B

Perkovic, V (2025). *NEJM, 392* (6), 531-543

How the 4-hit hypothesis may help guide clinical practice

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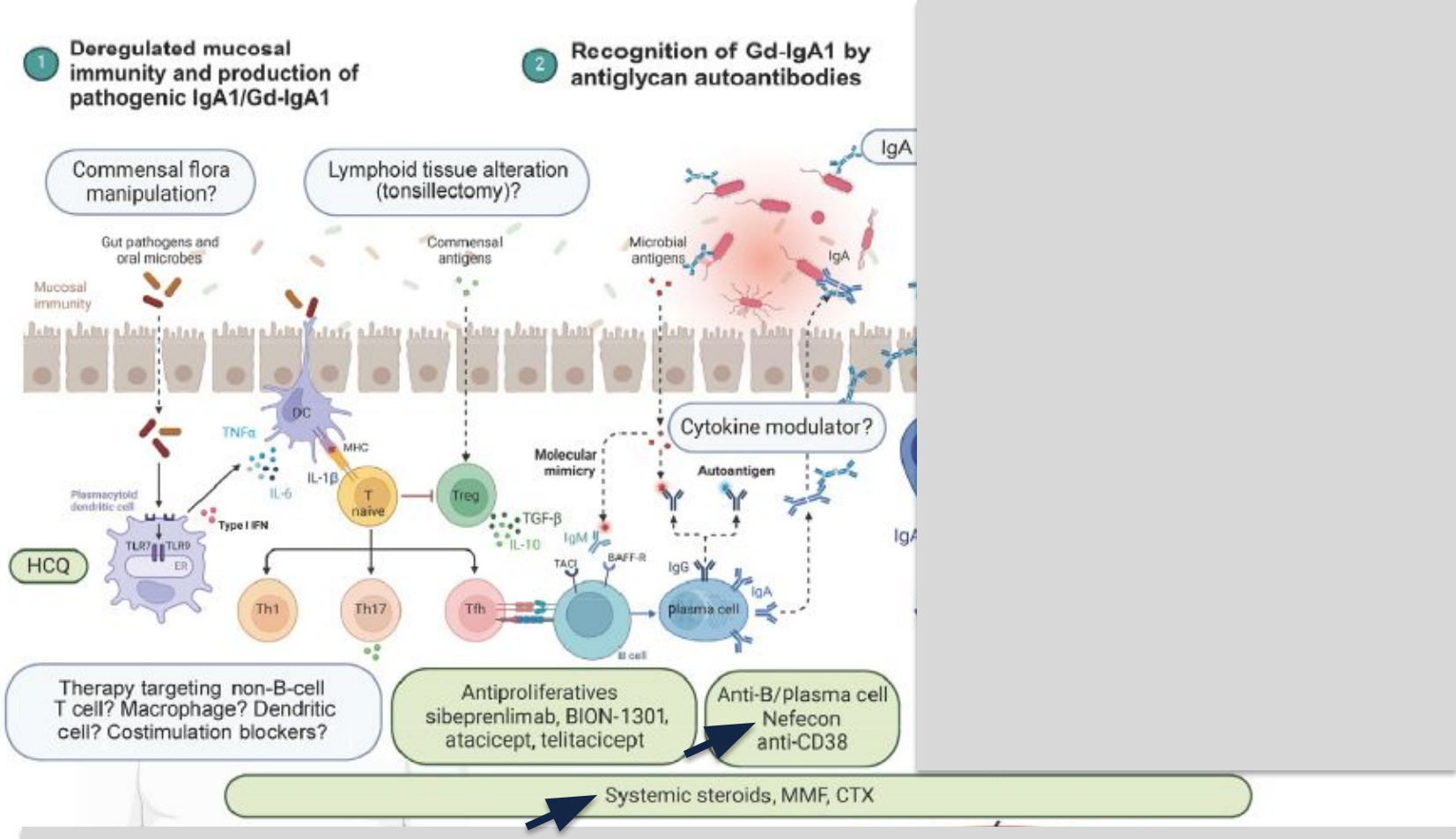
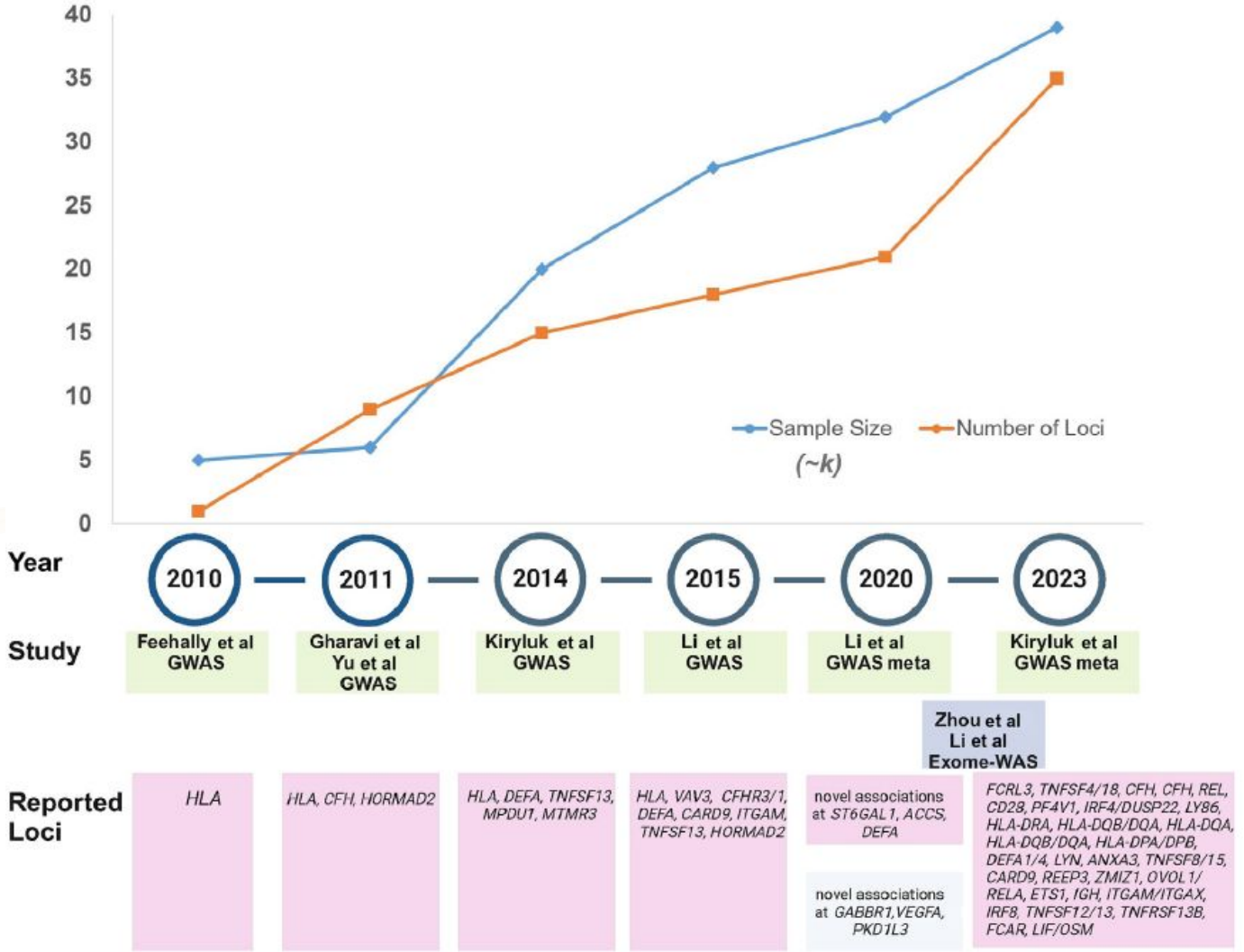
4 hit hypothesis holds potential for precision approaches



X Zhou, H Zhang *SeminNephrol* 44:151567 2025

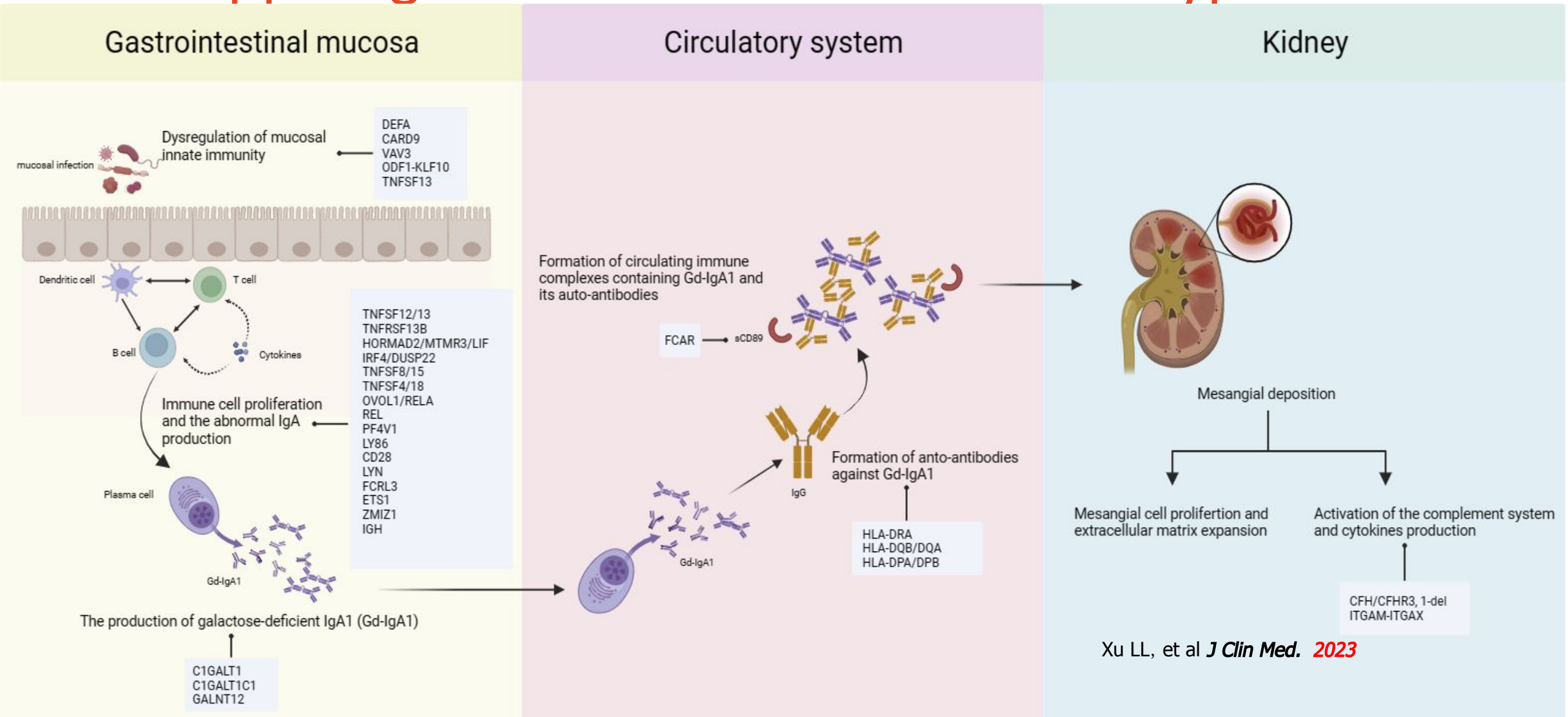
Meanwhile genetic understandings are growing



X Zhou, H Zhang *SeminNephrol* 44:151567 2025

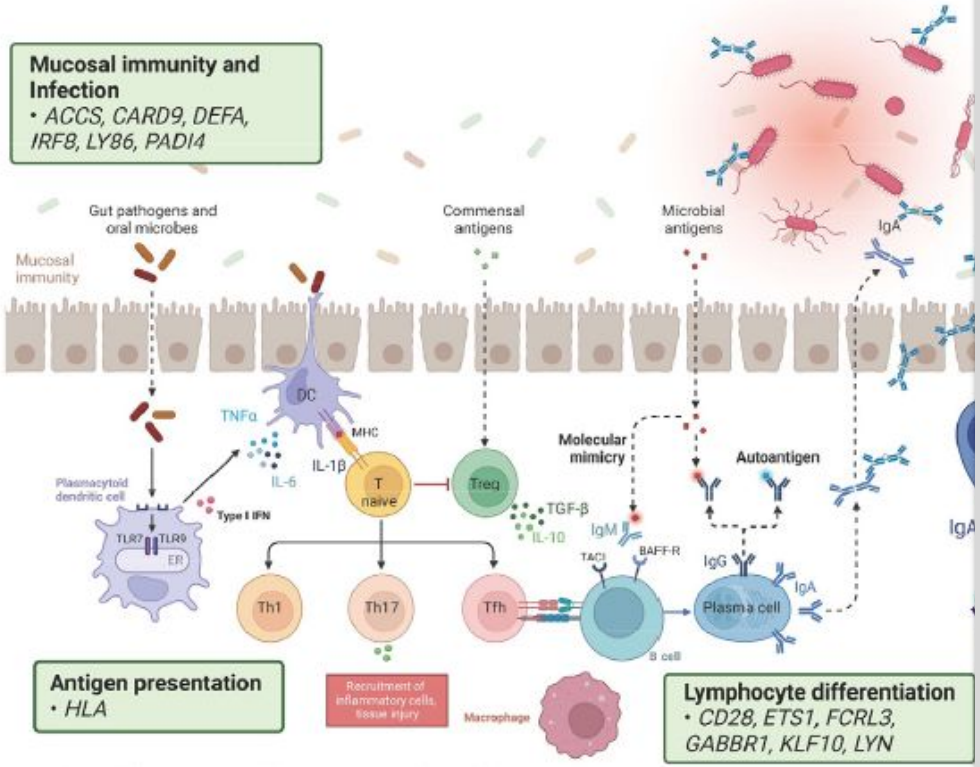
Milestone genome-wide association studies

IgAN is not a monogenic disease but GWAS data support genetic mutation in multihit hypothesis



Xu LL, et al *J Clin Med.* 2023

The 4 hit hypothesis holds potential for precision medicine approaches



Genes associated with IgAN are shown and grouped into the main pathogenic processes according to gene function

X Zhou, H Zhang *SeminNephrol* 44:151567 2025

Conclusions

- IgAN is a common and carries a high burden for individuals throughout much of the life span
- IgAN and its treatment requires input from multiple disciplines and is costly to health systems
- Accelerated regulatory approaches have stimulated pharmaceutical investment
- Rapidly evolving treatment landscape
  - SGLT2i, ERA, topical corticosteroids, B-cell and complement targeted treatments
  - New KDIGO guideline due 2025
- 4 hit theory of IgAN pathophysiology could provide a framework for tailored treatment regimens

THANK YOU!

Q&A

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