Preventing Kidney Function Decline and Failure in Patients With IgAN Through Earlier Diagnosis and Effective Intervention

This activity is provided by Integrity CE, LLC.
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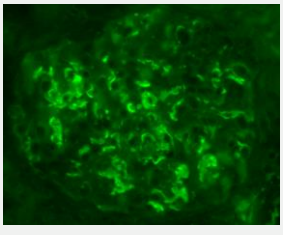
Learning Objectives

- Describe the pathophysiology of immunoglobulin A nephropathy (IgAN)
- Apply clinical guideline recommendations to achieve earlier diagnosis of IgAN
- Summarize clinical trial evidence regarding new and emerging therapies for IgAN that can delay the onset of kidney failure and reduce the side effects of conventional treatments
- Outline a treatment plan for patients with IgAN with declining kidney function despite optimal standard of care and steroid therapy

Overview, Burden, and Consequences of Delayed Diagnosis of IgAN

Overview of IgAN

- Progressive autoimmune disease characterized by deposition of IgA1-containing immune complexes in the glomerular mesangium
- Presentation ranges from asymptomatic to rapidly progressive glomerulonephritis
- Up to 50% of patients may develop kidney failure and the need for dialysis
- Initial treatment comprises aggressive supportive care (including RASi and SGLT2i therapy)
- Immunosuppression may be considered for high-risk patients
- Though not yet approved, several targeted therapies are currently under investigation

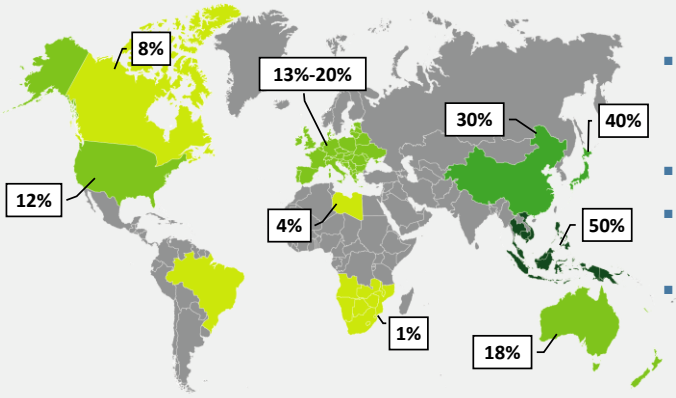


Mesangial IgA1 deposition

RASi, renin-angiotensin system inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

El Karoui K, et al. *J Am Soc Nephrol.* 2024;35(1):103-116; KDIGO. *Kidney Int.* 2021;100:S1-s276; Petrou D, et al. *Antibodies (Basel).* 2023;12(2):40.

The Prevalence of IgAN



- Most common primary glomerular disease worldwide
- Estimated annual incidence in the US is between 1.29 per 100,000 (all ages) and 2.5 per 100,000 (adults)
- Most common in East Asian individuals
- Common in White but relatively rare in Black individuals
- Male to female ratio:
  - 2:1 in North Americans and Western Europeans
  - 1:1 in East Asians

Caster DJ, et al. *Kidney Int Rep.* 2023;8:1792-1800; Stamellou E, et al. *Nat Rev Dis Primers*. 2023;9(1):67.

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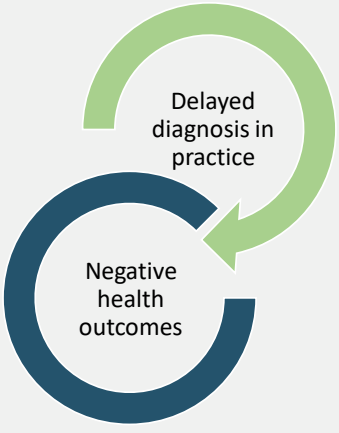
The Impact of IgAN on Mortality

Hastings et al. 2018*	Jarrick et al. 2019†
• Life expectancy substantially reduced for patients with IgAN (by ~10 years) • 83% of deaths occurred after progression to renal failure	• Patients with IgAN had increased mortality vs matched controls • One extra death per 310 person-years • 6-year reduction in life expectancy

Collective findings indicate IgAN increases mortality risk, with a shortening of life expectancy by 6-10 years. Importantly, excess mortality appears attributable to renal failure.

*Prospective southeastern US study. 251 adults with IgAN. Mean follow-up time: 19.3 years.
†Nationwide cohort study in Sweden. 3,622 patients with IgAN vs 18,041 matched general population controls. Median follow-up: 13.6 years.
Jarrick S, et al. *J Am Soc Nephrol*. 2019;30(5):866-876; Ștefan G, et al. *Medicina*. 2024;60(2):247.

Consequences of Delayed Diagnosis



- Diagnosis is typically prompted by gross or microscopic hematuria and/or proteinuria with or without abnormal renal function
- Diagnosis most commonly occurs between 25 and 40 years old
- **50% of adults are already at CKD stage 3 or greater at diagnosis**

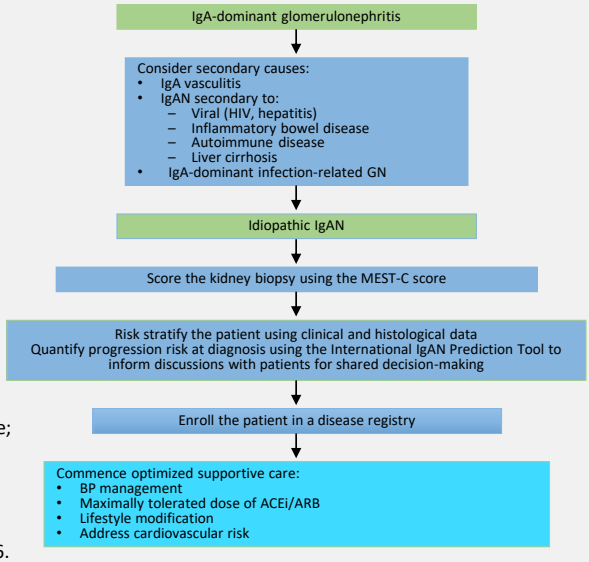
- Sustained exposure to elevated proteinuria (leading to renal damage and increased risk for progression)
- **Up to 50% of patients progress to KF within 20 years of diagnosis**
- **Kidney replacement may be required at a relatively young age**

CKD, chronic kidney disease; KF, kidney failure.

Berthoux FC, et al. *Semin Nephrol*. 2008;28(1):4-9; Caster DJ, et al. *Kidney Int Rep*. 2023;8:1792-1800; Hastings MC, et al. *Kidney Int Rep*. 2017;3(1):99-104; Knoop T, et al. *Nephrol Dial Transplant*. 2017;32(11):1841-1850; Le WB, et al. *Nephrol Dial Transplant*. 2012;27(4):1479-1485; McGrogan A, et al. *Nephrol Dial Transplant*. 2011;26(2):414-430; Moriyama T, et al. *PLoS One*. 2014;9(3):e91756. Reich HN, et al. *J Am Soc Nephrol*. 2007;18(12):3177-3183; Wyatt RJ, Julian BA. *N Engl J Med*. 2013;368(25):2402-2414.

Achieving Earlier Diagnosis and Assessment of Risk

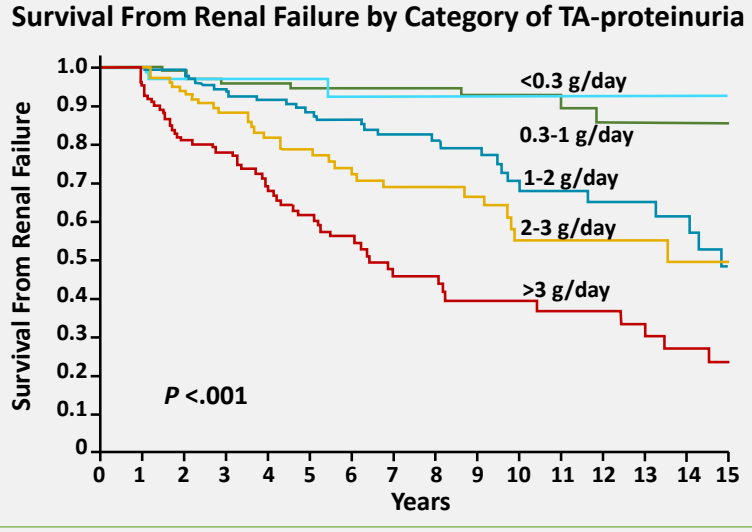
Evaluation of Suspected IgAN: 2021 KDIGO Guidelines



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BP, blood pressure; GN, glomerulonephritis; HIV, human Immunodeficiency virus; KDIGO, Kidney Disease Improving Global Outcomes.

KDIGO. *Kidney Int*. 2021;100:S1-s276.

Predicting Risk for Progression: Proteinuria



TA, time adjusted.

Reich HN, et al. *J Am Soc Nephrol.* 2007;18(12):3177-3183.

Predicting Risk for Progression: MEST-C Score

Histological Variable	Definition	Score
Mesangial hypercellularity	More than four mesangial cells in any mesangial area of a glomerulus	M0: <50% of glomeruli showing mesangial hypercellularity M1: >50% of glomeruli showing mesangial hypercellularity
Endocapillary hypercellularity	Hypercellularity due to an increased number of cells within glomerular capillary lumina	E0: no endocapillary hypercellularity E1: any glomeruli showing endocapillary hypercellularity
Segmental glomerulosclerosis	Adhesion or sclerosis (obliteration of capillary lumina by matrix) in part but not the whole glomerular tuft	S0: absent S1: present in any glomeruli
Tubular atrophy/ interstitial fibrosis	Estimated percentage of cortical area showing tubular atrophy or interstitial fibrosis, whichever is greater	T0: 0%–25% of cortical area T1: 26%–50% of cortical area T2: >50% of cortical area
Mesangial hypercellularity	More than four mesangial cells in any mesangial area of a glomerulus	M0: <50% of glomeruli showing mesangial hypercellularity M1: >50% of glomeruli showing mesangial hypercellularity

Markowitz G. *Nat Rev Nephrol.* 2017;13(7):385-386.

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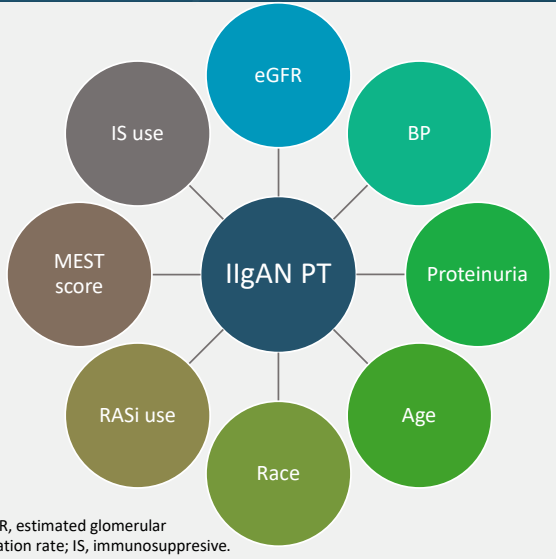
The International IgAN Prediction Tool



- Predicts risk of worsening kidney function over 5–7 years
- Can be used in adults of all ethnicities with primary IgAN
- Requires only routine clinical, laboratory, and biopsy information available at diagnosis

eGFR, estimated glomerular filtration rate; IS, immunosuppresive.
Barbour SJ, et al. *JAMA Inter Med.* 2019;179(7):942-952.

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Current Approach to Management of IgAN

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Supportive Care for IgAN

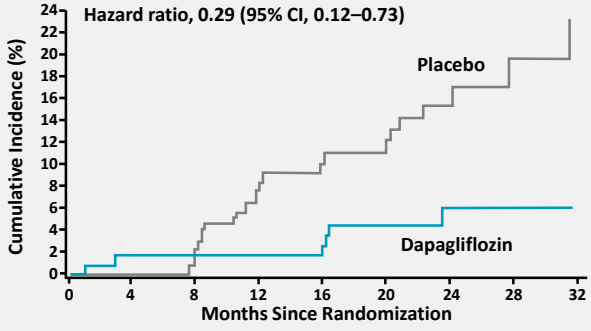
- Stringent BP control and management <120 mmHg for most patients
- Dietary sodium restriction <2 g/day
- ACEi/ARB if proteinuria >0.5 g/day (± hypertension)
- SGLT2i
- Lifestyle modification (weight normalization, smoking cessation, improve metabolic syndrome)
- Address CV risk
- Consider ETAR-B/ARB (sparsentan)

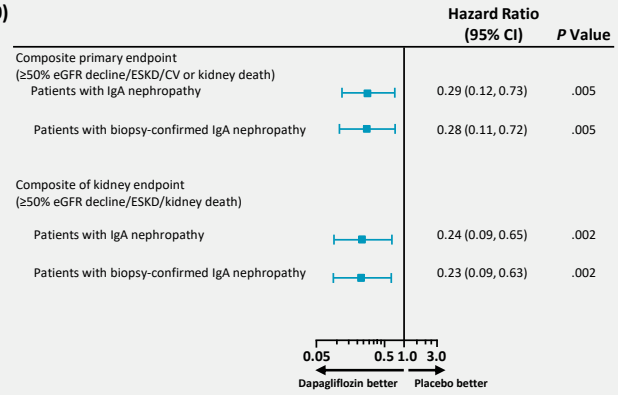
CV, cardiovascular; ETAR-B, endothelin type A receptor blocker.

KDIGO. *Kidney Int*. 2021;100:S1-s276; Stamellou E, et al. *Nat Rev Dis Primers*. 2023;9(1):67.

DAPA-CKD: SGLT2 Inhibition Reduces the Risk of CKD Progression in Patients With IgAN

Composite primary endpoint in patients with IgA nephropathy (n=270)



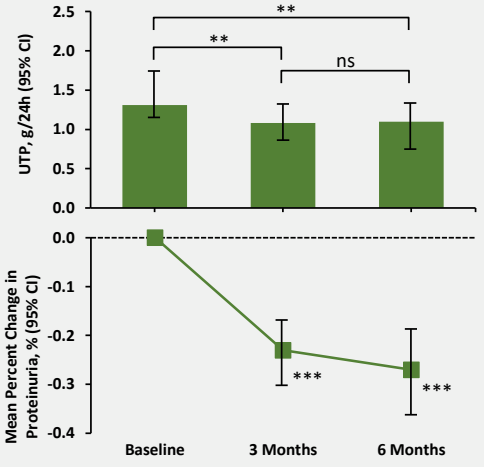


The primary composite endpoint (sustained decline in eGFR ≥50%, renal failure, or death from a kidney disease-related or CV cause) occurred in 4% patients on dapagliflozin and 15% on placebo (HR, 0.29; 95% CI, 0.12, 0.73).

CI, confidence interval; ESKD, end-stage kidney disease.

Wheeler DC, et al. *Kidney Int*. 2021;100(1):215-224.

SGLT2 Inhibitor Therapy Reduces Proteinuria in Patients With IgAN

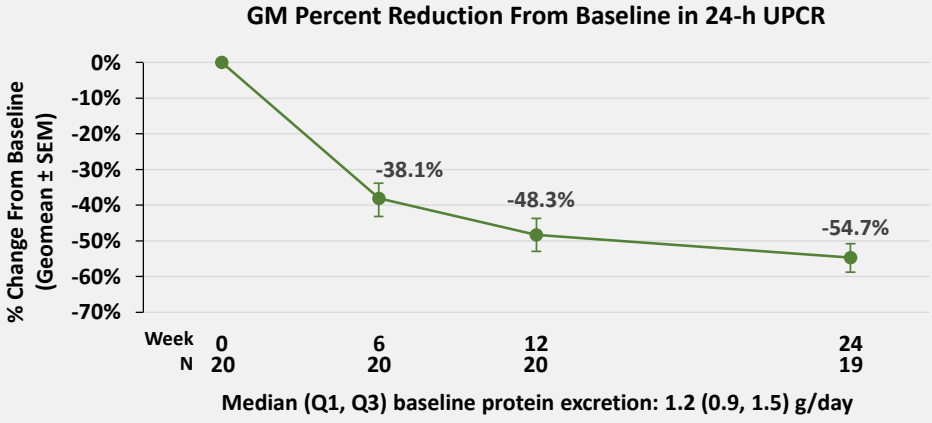


- SGLT2 inhibition* reduced proteinuria at 3m by **22.9%** (*P* < .001) and at 6m by **27.1%** (*P* <.001)
- At 6-m follow-up:
  - eGFR decreased by 3.0 mL/min/1.73m^2 (*P*=.012)
  - Albumin increased by 0.8 g/L (*P*=.017)
  - Antihypertensive effects not significant
  - Antiproteinuric effects observed independent of age, baseline proteinuria/eGFR, IS use, and presence of diabetes and HTN (all *P* values >.05)

*SGLT2i group, including dapagliflozin and canagliflozin; **P <.01; ***P <.001.
HTN, hypertension; m, months; UTP, urine proteinuria.

Dong Y, et al. *Front Med* (Lausanne). 2023;10:1242241.

AFFINITY: Efficacy and Safety of Atrasentan in Patients With IgAN



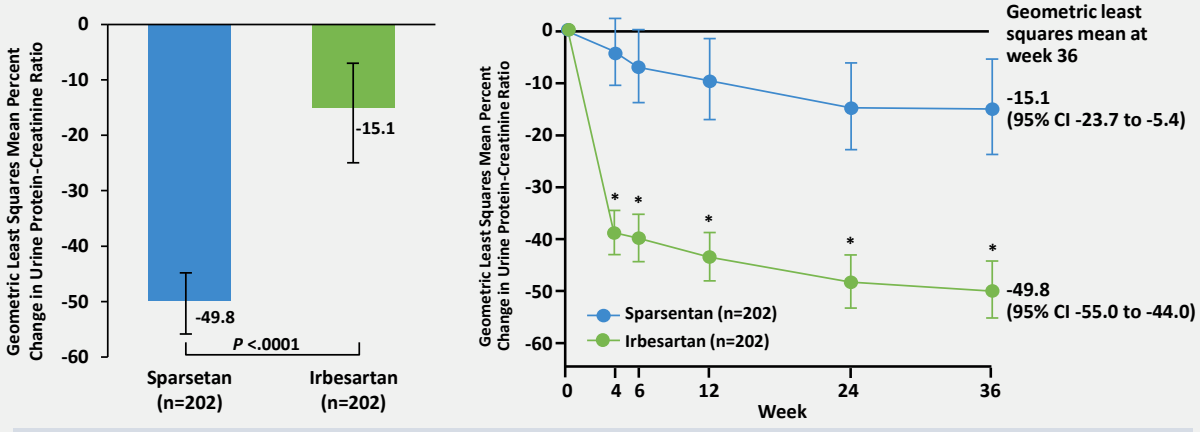
Median (Q1, Q3) baseline protein excretion: 1.2 (0.9, 1.5) g/day

Treatment with atrasentan resulted in a 48.3% and 54.7% reduction from baseline in 24-hour UPCR at weeks 12 and 24, respectively. Atrasentan was generally well-tolerated with no serious and no treatment-related AEs.

AE, adverse event; SEM, standard error of the mean; UPCR, urine protein creatinine ratio.

Kim SG, et al. *Kidney Int Rep.* 2023;8(9):1902.

PROTECT: Efficacy and Safety of Sparsentan in Patients With IgAN (Interim Analysis)



At week 36, treatment with sparsentan vs irbesartan was associated with a greater decrease from baseline in UPCR (–49.8% vs –15.1%; *P* <.0001). TEAEs were similar between groups with no cases of SAE-related discontinuations.

**P* <.0001 for sparsentan vs irbesartan at each week. SAE, serious adverse event, TEAE, treatment-emergent adverse event.

Heerspink HJL, et al. *Lancet*. 2023;401(10388):1584-1594.

Corticosteroids: Overview of Clinical Trial Evidence

STOP-IgAN

- Supportive care alone vs supportive care plus IS therapy after 6m run-in
- Add-on IS therapy resulted in higher clinical remission rate but more AEs
- Proteinuria improved with IS therapy but did not result in kidney function preservation

TESTING Trial

- Methylprednisolone vs PBO after 6m run-in
- Intervention was altered due to an excess of SAEs (methylprednisolone dose was lowered and prophylaxis against pneumocystis pneumonia was administered)
- Steroid treatment associated with renal benefit (composite of 40% eGFR decline/renal failure/death from kidney failure) and reduced proteinuria in the full-dose but increased the incidence of SAEs
- In the reduced-dose cohort, renal benefits were also observed (though to a lesser extent) and SAE incidence was lower

PBO, placebo.

Lv J, et al. *JAMA*. 2022;327(19):1888-1898; Rauen T, et al. *N Eng J Med.* 2015;373(23):2225-2236.

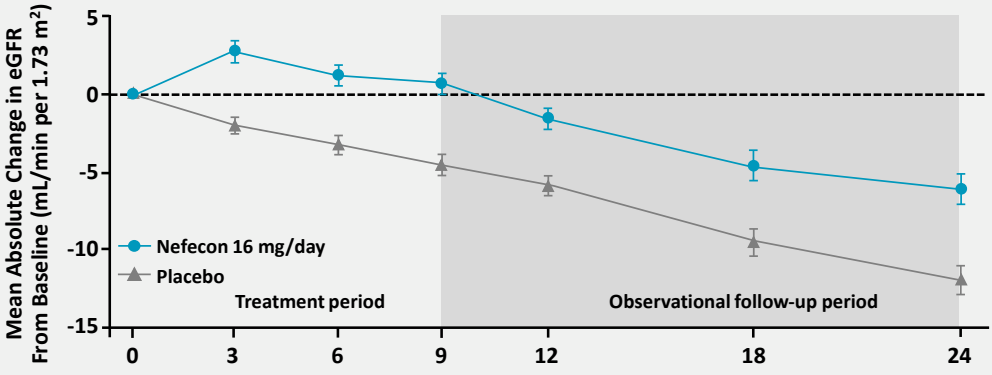
Contraindications Against Glucocorticoid Treatment

- eGFR <30 mL/min/1.73m^2
- Diabetes
- Obesity (BMI >30 kg/m^2)
- Latent infection (eg, viral hepatitis, TB)
- Secondary disease (eg, cirrhosis)
- Active peptic ulceration
- Uncontrolled psychiatric illness
- Severe osteoporosis

BMI, body mass index; TB, tuberculosis.

KDIGO. *Kidney Int*. 2021;100:S1-s276.

NefIgArd Trial: Targeted-release Budesonide



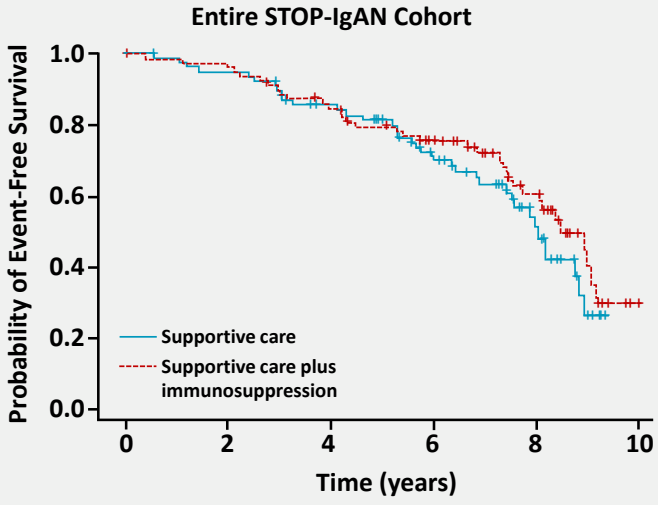
Renal function was improved over 2 years with TRF-B vs PBO; the time-weighted average change with TRF-B vs PBO was -2.47 vs -7.52 mL/min per 1.73 m², respectively (*P* <.0001). The most common TEAEs were peripheral edema, HTN, muscle spasms, acne, and headache. No treatment-related deaths were reported.

TRF-B, targeted-release formulation of budesonide.

Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

IgAN Pathophysiology

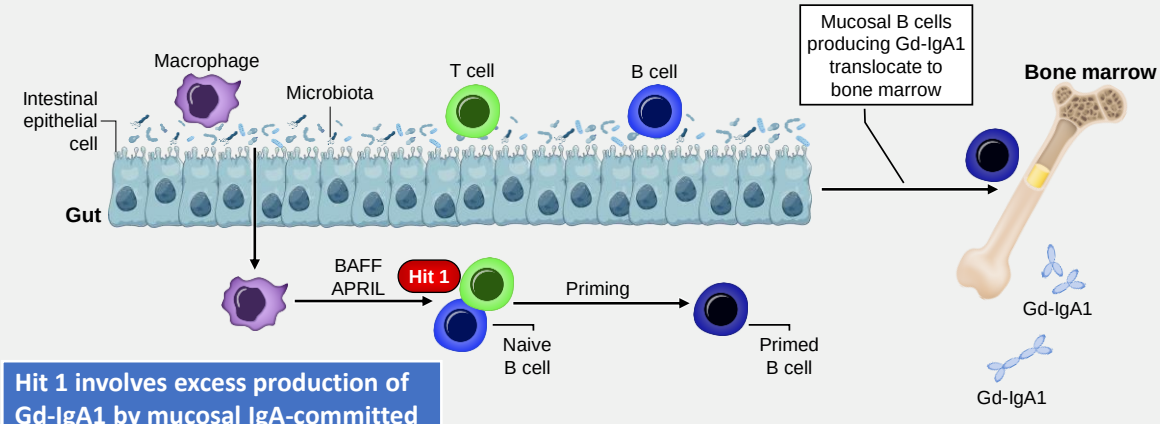
Targeting the Pathophysiology of IgAN: An Unmet Need in Treatment



- Even with aggressive supportive care (with or without IS), patients with IgAN continue to experience disease progression and low probability of event-free survival
- Therapies to address formation of pathogenic Gd-IgA1 containing immune complexes are needed to address underlying drivers of disease

Gd, galactose deficient.
Rauen T, et al. *Kid Int.* 2020;98(4):1044-1052.

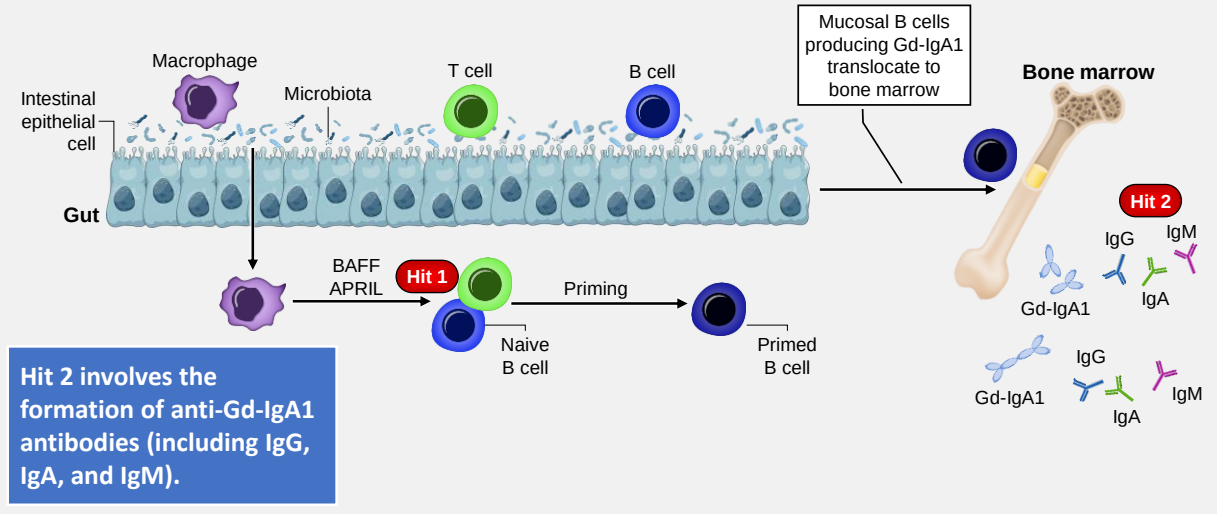
The Pathogenesis of IgAN: Hit 1



Hit 1 involves excess production of Gd-IgA1 by mucosal IgA-committed B cells, which translocate to the bone marrow.

APRIL, A proliferation-inducing ligand; BAFF, B-cell activation factor.
Stamellou E, et al. *Nat Rev Dis Primers.* 2023;9(1):67.

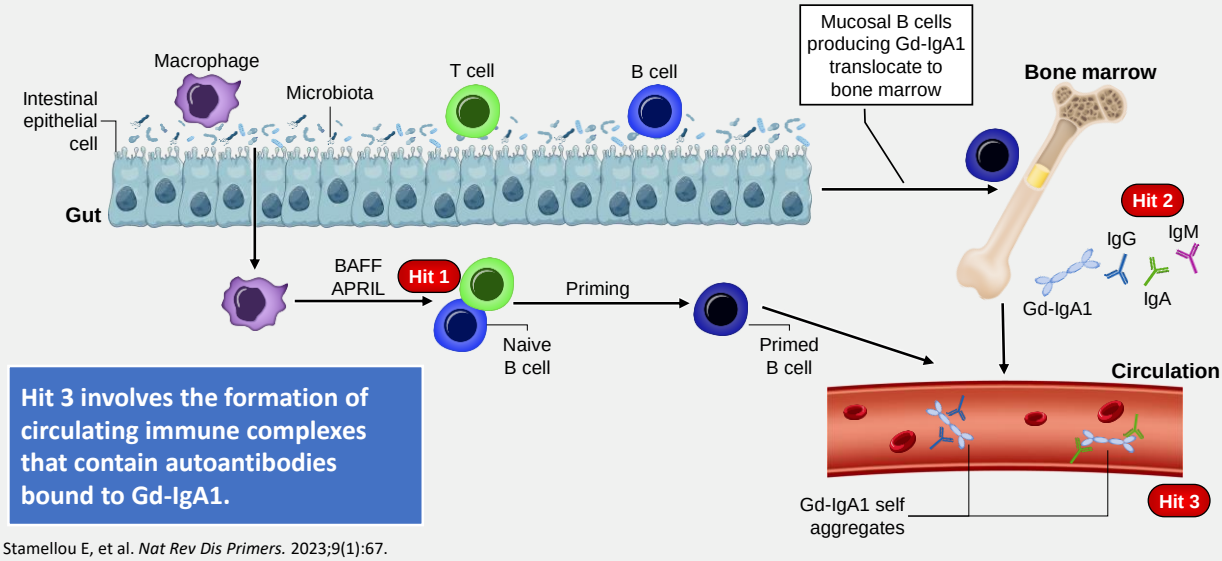
The Pathogenesis of IgAN: Hit 2



Hit 2 involves the formation of anti-Gd-IgA1 antibodies (including IgG, IgA, and IgM).

Ig, immunoglobulin.
Stamellou E, et al. *Nat Rev Dis Primers.* 2023;9(1):67.

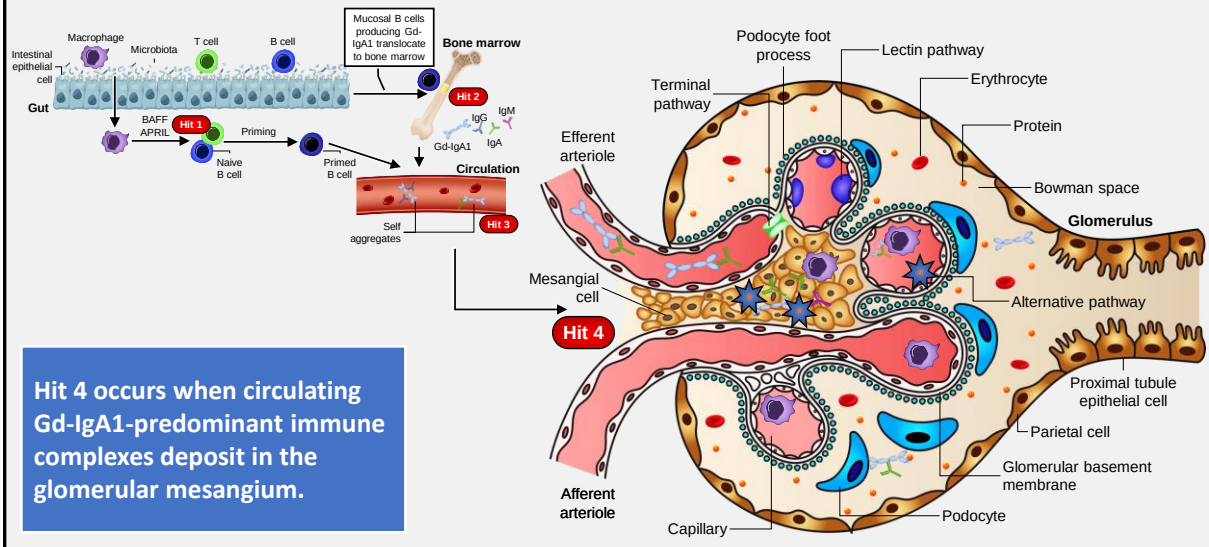
The Pathogenesis of IgAN: Hit 3



Hit 3 involves the formation of circulating immune complexes that contain autoantibodies bound to Gd-IgA1.

Stamellou E, et al. *Nat Rev Dis Primers.* 2023;9(1):67.

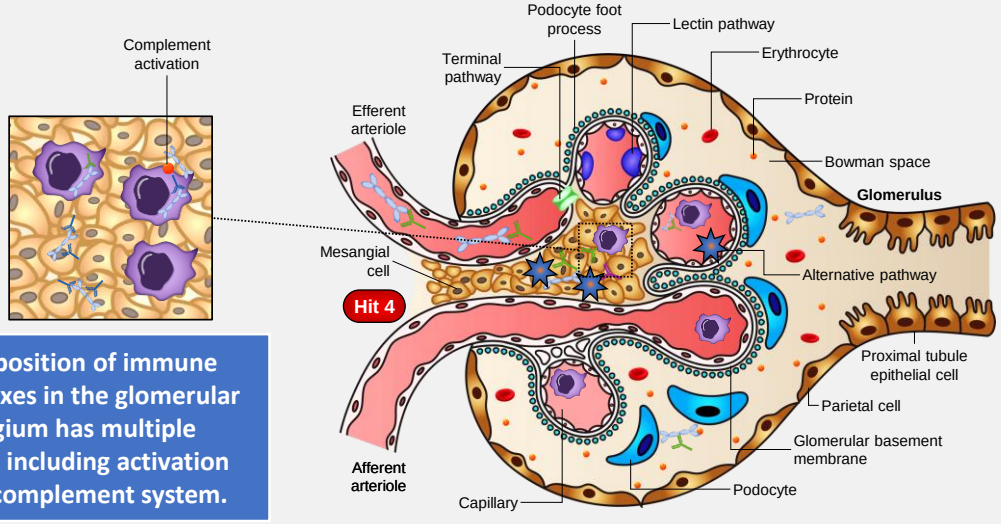
The Pathogenesis of IgAN: Hit 4



Hit 4 occurs when circulating Gd-IgA1-predominant immune complexes deposit in the glomerular mesangium.

Stamellou E, et al. *Nat Rev Dis Primers.* 2023;9(1):67.

The Pathogenesis of IgAN: Complement Activation



The deposition of immune complexes in the glomerular mesangium has multiple effects, including activation of the complement system.

Stamellou E, et al. *Nat Rev Dis Primers.* 2023;9(1):67.

Emerging Therapies for IgAN Treatment

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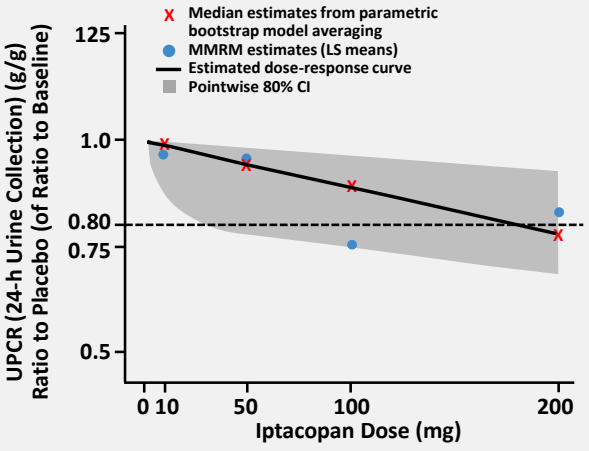
Overview of Emerging Therapies in Phase 3 That Target IgAN Pathogenesis

Therapeutic Strategy	Agent	Target	Phase 3 Trial	Estimated Completion
Complement system-targeting	Iptacopan	B factor	NCT04578834 (APPLAUSE-IgAN)	10/2025
	Ravulizumab	C5	NCT06291376 (I CAN)	10/2029
B-cell targeting	Telitacicept	BLyS/APRIL	NCT05799287	12/2025
	Sibeprenlimab*	APRIL	NCT0524864 (VISIONARY Study)	12/2026
	Zigakibart	APRIL	NCT05852938 (The BEYOND Study)	5/2028
	Atacicept	BLyS/APRIL	NCT04716231 (ORIGIN 3)	7/2028

*Granted Breakthrough Therapy designation for IgAN by the FDA in 2024.
BlyS, B-lymphocyte stimulator.
Available at: https://clinicaltrials.gov/

Efficacy and Safety of Iptacopan in Patients With IgAN



- Iptacopan treatment resulted in:
  - Dose response effect vs PBO on UPCR reduction at 3 m (*P*=.038)
  - Reduction of 23% (80% CI: 8%–34%) from baseline in UPCR vs PBO (200 mg dose; MCP-Mod estimate = 0.77; 80% CI 0.66–0.92)
  - Strong alternative complement pathway inhibition
  - Persistent proteinuria reduction
- Treatment was well-tolerated, with no reports of deaths, SAEs, or bacterial infections

LS, least squares; MCP-Mod, multiple comparison procedure – modeling; MMRM, mixed model repeated measures.

Zhang H, et al. *Kidney Int*. 2024;105(1):189-199.

APPLAUSE-IgAN: Efficacy of Iptacopan in Patients With IgAN (Interim Results)

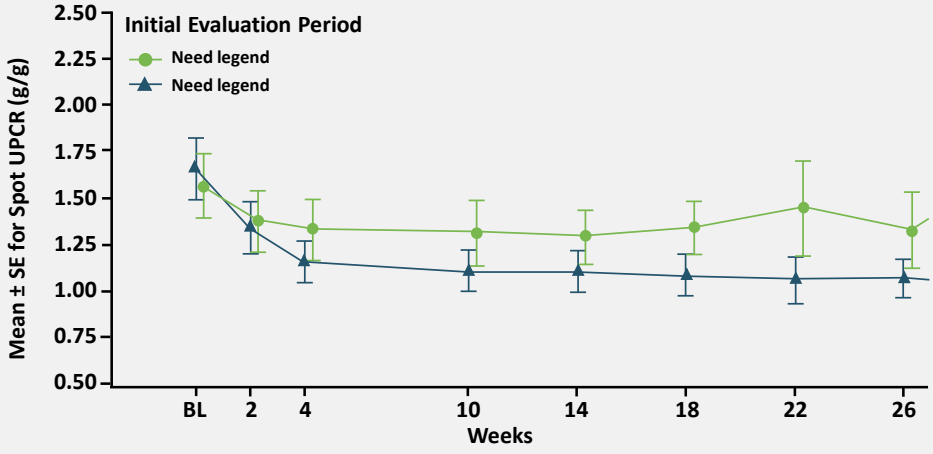
Repeated Measures Analysis of Log Ratio to Baseline in UPCR (From 24-hour Urine Collection) at 9 months

	Treatment	n/N	Geometric Adjusted Mean (95% CI)	Iptacopan 200 mg BID vs Placebo		
				Geometric Mean Ratio % (95% CI)	% Reduction (95% CI)	1-Sided *P*-Value
Month	Iptacopan	118/125	0.562 (0.491, 0.642)	0.617 (0.514, 0.740)	38.3 (26.0, 48.6)	<.0001*
	Placebo	106/125	0.910 (0.792, 1.046)			

BID, twice daily.

Perkovic V, et al. *Kidney Int Rep*. 2024;9(4):S506.

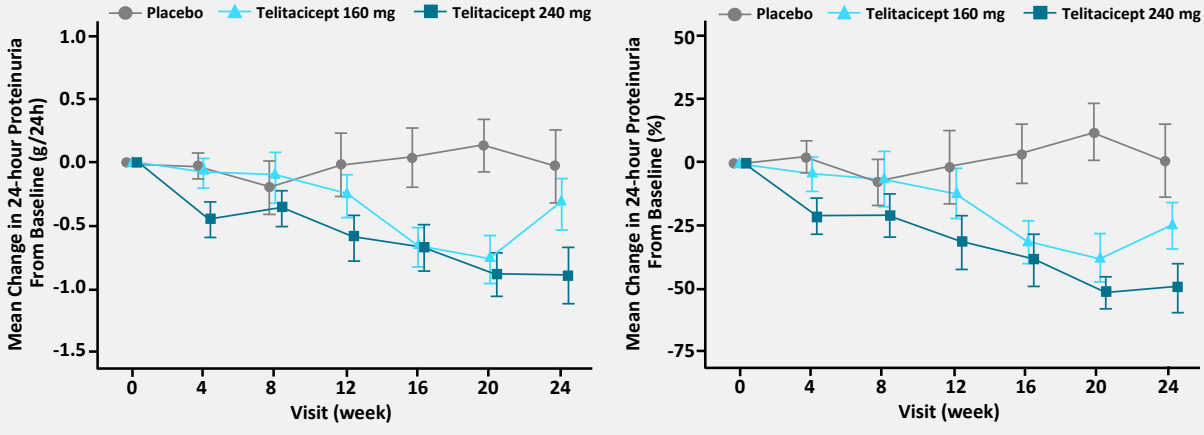
Efficacy and Safety of Ravulizumab in Patients With IgAN (Phase 2 Results)



At 26 weeks, ravulizumab treatment resulted in rapid and sustained proteinuria reduction that was greater as compared with PBO (40.3% vs 10.9%; *P*=.0012). The safety profile of ravulizumab was similar to PBO.

Barratt J, et al. *Kidney Int Rep.* 2024;9(4):S155-S156.

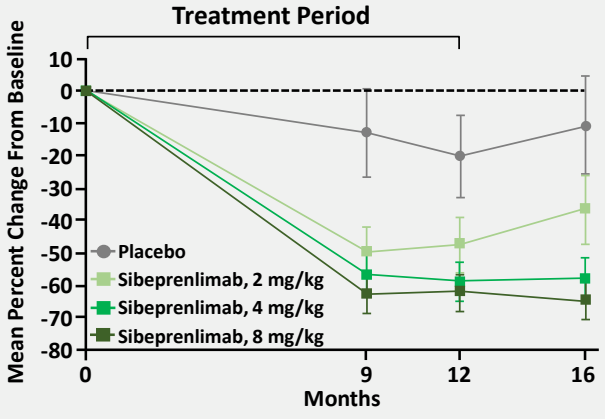
Dual Inhibition of BlyS and APRIL With Telitacicept in Patients With IgAN



Treatment with telitacicept reduced mean proteinuria by 49% (240-mg dose; *P*=.013) and 25% (160-mg dose; *P*=.389) from baseline. TEAEs were similar across groups and were mild or moderate.

Lv J, et al. *Kidney Int Rep.* 2023;8(3):499-506.

Phase 2 ENVISION Trial: Efficacy and Safety of APRIL Inhibition With Sibeprenlimab in Patients With IgAN

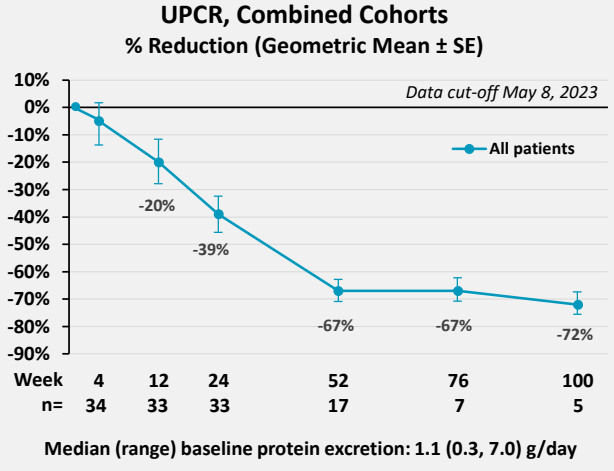


- After 12 months, treatment with sibeprenlimab decreased UACR from baseline; reductions in 24-h UACR from baseline were 47.2%, 58.8%, 62.0%, and 20.0% in the 2 mg, 4 mg, 8 mg, and PBO groups, respectively (*P* <.001)
- AE incidence after treatment initiation was 78.6% and 71.1% in the pooled sibeprenlimab and PBO groups, respectively

UACR, urine albumin-creatinine ratio.

Mathur M, et al. *N Engl J Med*. 2024;390(1):20-31.

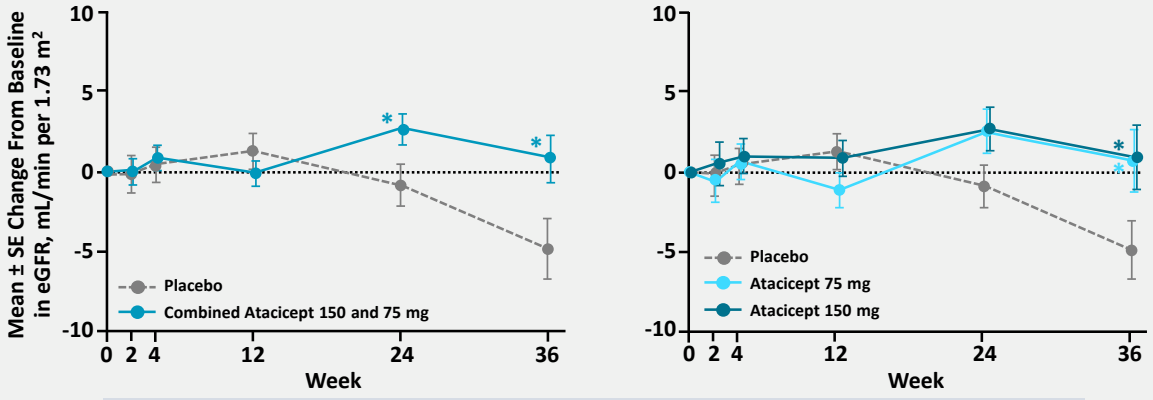
A Phase 1/2 Study Of the Anti-APRIL Zigakibart in Patients With IgAN



- Zigakibart treatment resulted in the following in both cohorts:
  - UPCR reductions by Week 12 across baseline proteinuria levels
  - Significant and durable reductions in serum Gd-IgA1 concentrations
  - Durable reductions in serum levels of free APRIL and immunoglobulins
- Treatment was well-tolerated, with no SAEs or AE-related terminations

Barratt R, et al. *Nephrol Dial Transplant*. 2023;38(suppl 1):4057.

Efficacy and Safety of the Dual BlyS and APRIL Inhibitor Atacicept for the Treatment of IgAN

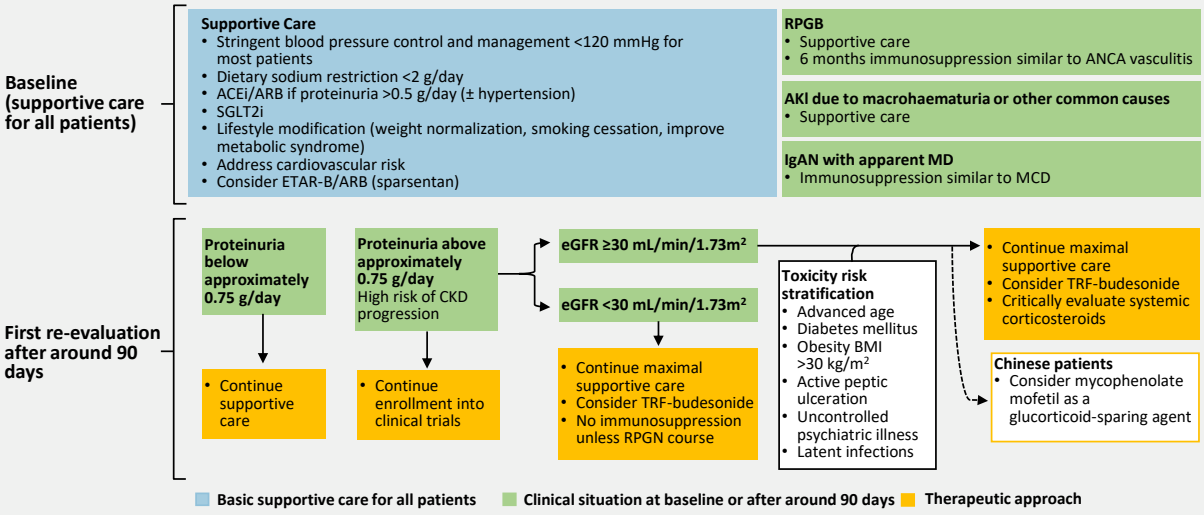


Treatment with atacicept (combined 150 and 75 mg groups) significantly reduced UPCR from baseline as compared with placebo at 24 weeks (25% reduction; *P*=.037) and 36 weeks (35% reduction; *P*=.0042; [graph]). The safety profile of atacicept was similar to placebo.

Lafayette R, et al. *Kidney Int*. 2024;105(6):1306-1315.

Creating a Treatment Plan

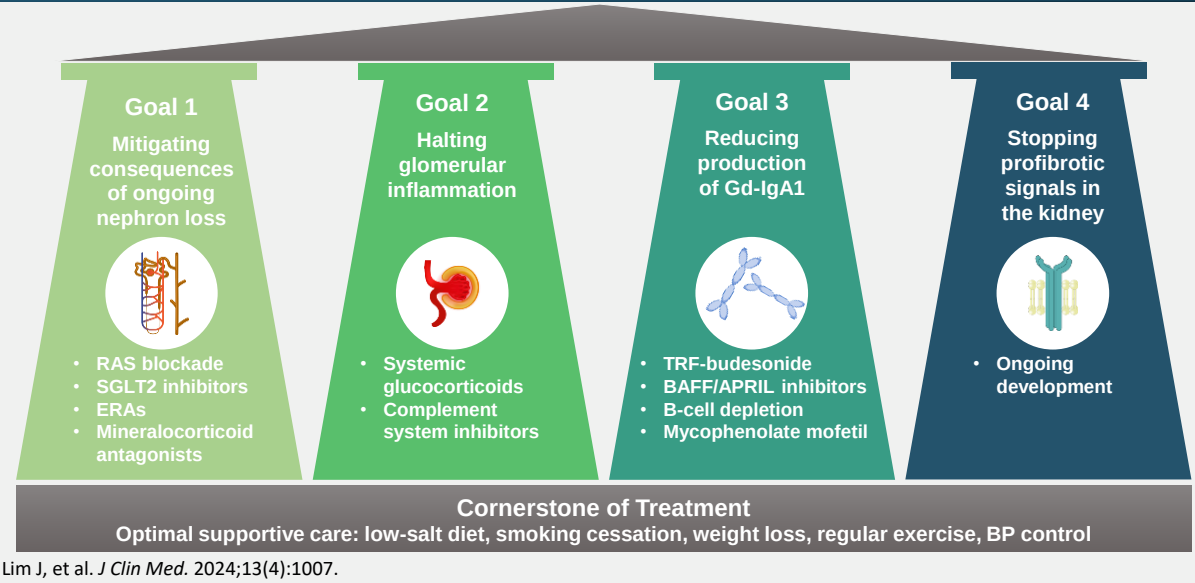
Modified KDIGO 2021 Therapeutic Algorithm



AKI, acute kidney injury; ANCA; antineutrophil cytoplasmic antibody; MCD, minimal change disease; RPGN, rapidly progressive glomerulonephritis.

Stamellou E, et al. *Nat Rev Dis Primers.* 2023;9(1):67.

The Pillars of IgAN Treatment



Lim J, et al. *J Clin Med.* 2024;13(4):1007.

Concluding Remarks

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Summary of Key Points

- IgAN is a progressive autoimmune kidney disease that ranges widely in clinical presentation from a lack of recognizable symptoms to the onset of kidney failure
- Patients are often undiagnosed until irreversible kidney damage has occurred and therefore clinicians should maintain a high index of suspicion for the disease
- Improved understanding of IgAN pathogenesis has led to development of novel strategies to preserve renal function and reduce the risk for poor outcomes, including kidney failure and mortality
- Though initial treatment continues to consist of supportive care that includes pharmacologic therapy, expanded options now include SGLT2i's and ERAs
- Several novel targeted therapies are also in development for high-risk disease, offering potential alternatives to immunosuppressive therapy, which is associated with serious adverse effects when used long-term

Thank You!

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