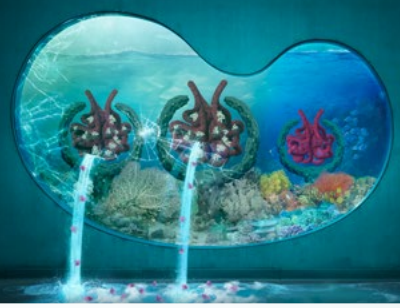
Target Proteinuria

IgA NEPHROPATHY (IgAN) EXPLAINED



EPIDEMIOLOGY

IgAN is the most prevalent primary glomerulonephritis worldwide[1]

- Registry data show a mean age at diagnosis of **~42 years**[2]
- **2.5/100,000** people affected globally per year[3]
- Detected in **19–51%** of kidney biopsies in Europe[4]

A kidney biopsy is required for confirmation of IgAN diagnosis[1]

IgAN is asymptomatic for many patients, but some may present with symptoms such as:[5–7]

- Proteinuria
- Macro- or microhematuria
- Renal insufficiency
- Hypertension
- Edema
- Acute kidney injury

PATHOPHYSIOLOGY

The pathogenesis of IgAN is often described by the "4 Hits" hypothesis:[10]

Hit 1: Aberrant glycosylation of IgA_1 results in increased circulating galactose-deficient (Gd)–IgA_1

Hit 2: Production of anti-glycan antibodies that recognize Gd–IgA_1

Hit 3: Formation of pathogenic IgA_1-containing circulating immune complexes

Hit 4: Mesangial deposition and activation of mesangial cells resulting in glomerular injury

...compromised glomerular filtration barrier leading to proteinuria[5,11–13]

This deposition increases the production of **endothelin 1 (ET-1) and angiotensin II (ANG II)**, which act in tandem to amplify inflammation and damage to the glomerular filtration barrier and tubulointerstitial compartment, leading to increased proteinuria and ultimately kidney failure[13–15]

DISEASE PROGRESSION

IgAN is a long-term, progressive disease with a relentless clinical course[2,5,6]

The approximate age of kidney failure or death is 48[2]

In the RaDaR IgAN cohort, 50% of patients reached kidney failure or died[2]*

At diagnosis, 2/3 of patients are already at chronic kidney disease (CKD) stage ≥3[2,8]

In IgAN, proteinuria is the strongest modifiable predictor of the rate of disease progression[2,9]

TREATMENT GOALS

To reduce the rate of **loss of kidney function to the physiological state (<1 mL/min/year)** for the rest of the patient's life[1]

by maintaining urine protein excretion at <0.5 g/day or ideally <0.3 g/day[1†]

IgAN is often silent, yet even patients with proteinuria <0.5 g/day **remain at risk of disease progression** and **irreversible kidney function loss[2]**

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*RaDaR is a UK based rare kidney disease registry, with an IgAN cohort of 2,439 patients, 2,299 adults and 140 children, forming the study population of this analysis. Patients eligible for enrolment had biopsy-proven IgAN, with proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m^2 at any time in the history of their disease.[1]

†In some patients with extensive kidney scarring this may not be possible and multiple treatment strategies are likely to be needed to achieve this.[1]

ANG II, angiotensin II; **CKD,** chronic kidney disease; **eGFR,** estimated glomerular filtration rate; **ET-1,** endothelin 1; **Gd,** galactose–deficient; **IgA,** immunoglobulin A; **IgA_1,** Immunoglobulin A subclass 1; **IgAN,** immunoglobulin A nephropathy; **KDIGO,** Kidney Disease: Improving Global Outcomes; **RaDaR,** UK National Registry of Rare Kidney Diseases; **UK,** United Kingdom.

1. Kidney Disease: Improving Global Outcomes (KDIGO) IgAN and IgAV Work Group. *Kidney Int.* 2025;108(4S):S1–S71. **2.** Pitcher D, *et al. Clin J Am Soc Nephrol.* 2023;18(6):727–38. **3.** McGrogan A, *et al. Nephrol Dial Transplant.* 2011;26:414–30. **4.** Coppo R. *Kidney Dis.* 2018;4:58–64. **5.** Wyatt R, Julian B. *N Engl J Med.* 2013;368:2402–14. **6.** Lai KN, *et al. Nat Rev Dis Primers.* 2016;2:16001. **7.** Penfold RS, *et al. Int J Nephrol Renovasc Dis.* 2018;11:137–4811. **8.** Caster D, *et al. Kidney Int Rep.* 2023;8:1792–800. **9.** Reich HN, *et al. J Am Soc Nephrol.* 2007;18:3177–83. **10.** Suzuki H, *et al. J Am Soc Nephrol.* 2011;22:1795–1803. **11.** Barratt J, Feehally J. *J Am Soc Nephrol.* 2005;16:2088–97. **12.** Boyd J, *et al. Kidney Int.* 2012;81:833–43. **13.** Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol.* 2016;310:R877–84. **14.** Kohan DE, Barton M. *Kidney Int.* 2014;86:896–904. **15.** Raina R, *et al. Kidney Dis.* 2020;6:22–34.

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