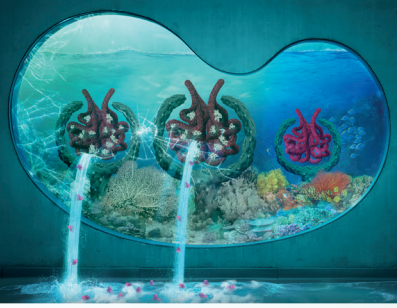
Target Proteinuria

IgA NEPHROPATHY (IgAN) EXPLAINED



EPIDEMIOLOGY

IgAN is the most prevalent primary glomerulonephritis worldwide[1]

- Mean age at **diagnosis is 41**[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]

Risk factors include:[5–8]

- Genetic
- Environmental
- Lifestyle factors

DISEASE PROGRESSION

IgAN is a long-term, progressive disease with a relentless clinical course[2,9]

- **The median age of kidney failure or death is 48**[2]
- **Over a median follow-up of 9.5 years, 51% of adult patients (N=2168) progressed to ESKD**[10]*
- **At diagnosis, 2/3 of patients are already at CKD stage ≥3**[2,11]
- **Sustained proteinuria of >1g/day is the strongest modifiable predictor of the rate of progression in IgAN**[12]

PATHOPHYSIOLOGY

There are 4 Hits involved in the pathogenesis of IgAN:[5]

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[13–15]

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[16–18]

TREATMENT TARGETS

According to the KDIGO guidelines, the reduction of proteinuria is a key treatment target in IgAN:[1]

Full remission **<0.3g** per day

However, with current supportive care **63%** of patients† (N=96) **DO NOT reach the KDIGO recommended target** with treatment[19]

There are limited treatment options indicated for IgAN, such as generically used renin-angiotensin-aldosterone system (RAAS) inhibition and glucocorticoids, which leaves patients at high risk of progression[19‡]

THERE IS A HIGH CLINICAL UNMET NEED FOR DISEASE COURSE MODIFYING TREATMENTS THAT PRESERVE KIDNEY FUNCTION FOR PATIENTS WITH IgAN

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*UK-based study of biopsy-verified patients with IgAN (N=2,168).[10] †Prospective study of patients with biopsy-proven IgAN (urinary protein ≥1g/day). 63.5% of patients treated with an ACEi or ARB did not achieve remission after 3 months of treatment. Partial remission (defined as <1g/day and ≥50% decrease from baseline with stable kidney function [≤25% reduction in eGFR]) of proteinuria was seen in 29 patients (30.2%) after 3 months of treatment.[18] ‡The KDIGO Guidelines define high risk of progression in IgAN as proteinuria >0.75–1g/day, despite at least 90 days of optimized supportive care[1]

ACEi, angiotensin-converting-enzyme inhibitor; **ANG II,** angiotensin II; **ARB,** angiotensin receptor blocker; **CKD,** chronic kidney disease; **eGFR,** estimated glomerular filtration rate; **ESKD,** end-stage kidney disease; **ET-1,** endothelin-1; **Gd,** galactose–deficient; **IgA,** immunoglobulin A; **IgA_1,** Immunoglobulin A subclass 1; **IgAN,** IgA nephropathy; **KDIGO,** Kidney Disease: Improving Global Outcomes; **RAAS,** renin-angiotensin-aldosterone system

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100:S1–276. **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.** Suzuki H, *et al. J Am Soc Nephrol* 2011;22:1795–803. **6.** Maiguma M, *et al. PLoS One* 2014;9:e90558. **7.** Coppo R. *Nephrol Dial Transplant* 2015;30:360–6. **8.** Yuzawa Y, *et al. Clin Exp Nephrol* 2016;20:511–35. **9.** Lai K, *et al. Nat Rev Dis Primers* 2016;2:16001. **10.** Barratt J, *et al. ASN* 2021; poster presentation (PO1577). **11.** Caster D, *et al. Kidney Int Rep* 2023;8:1792–800. **12.** Reich HN, *et al. J Am Soc Nephrol* 2007;18:3177–83. **13.** Wyatt R, Julian B. *N Engl J Med* 2013;368:2402–14. **14.** Barratt J, Feehally J. *J Am Soc Nephrol* 2005;16:2088–97. **15.** Boyd J, *et al. Kidney Int* 2012;81:833–43. **16.** Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016;310:R877–84. **17.** Kohan DE, Barton M. *Kidney Int* 2014;86:896–904. **18.** Raina R, *et al. Kidney Dis* 2020;6:22–34. **19.** Bagchi S, *et al. Kidney Int Rep* 2021;6(6):1661–8.

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