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TOGETHER, WE CAN CHANGE THE TUNE

FOR IgA NEPHROPATHY PATIENTS

Act on the two fundamental drivers of nephron loss in IgA nephropathy[1]

Fictional character and image co-created using AI.

IgA, immunoglobulin A.

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IgA nephropathy is heterogeneous and progressive with a significant burden of disease[1–3]

IgA nephropathy is the most common primary glomerulonephritis worldwide,[4] with an annual incidence of 7.9–26 per million in Europe,[5–10] 7–21 per million in the USA[11,12] and 5.5–45 per million in East Asia.[13–16]

Clinical presentation is heterogeneous, and patients face a range of challenging symptoms compounded by an unpredictable disease course and the fear of progression to kidney failure.[1–3,17]

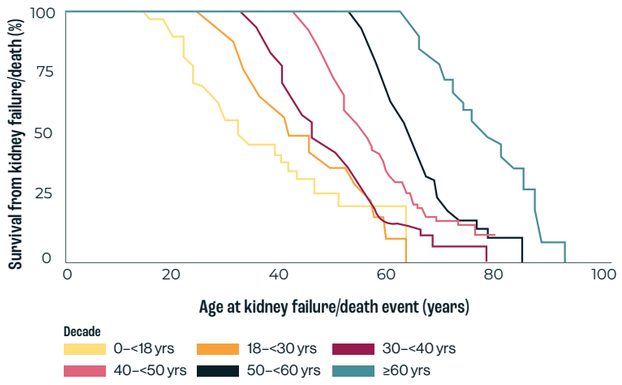
Treatment has historically focused on supportive care, including RASi and immunosuppression.[18] Despite this, most patients are expected to progress to kidney failure within 10–15 years of diagnosis.*[19]

Early identification and intervention with a targeted treatment approach are crucial to preserve kidney function for as long as possible[19,20]

48 YEARS

Mean age at kidney failure/death[19]

Kaplan-Meier survival curves of time to kidney failure/death by age at diagnosis*[19]



Adapted from Pitcher D, et al. Clin J Am Soc Nephrol. 2023.[19]

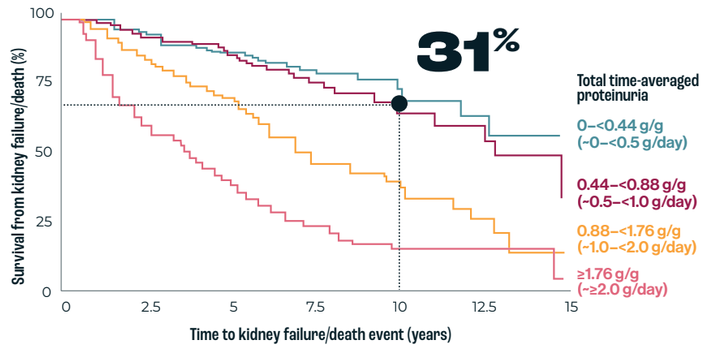
* Data from a retrospective cohort of the UK National Registry of Rare Kidney Diseases (RaDaR) (N=2439). Patients enrolled had a biopsy-proven diagnosis of IgA nephropathy plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73m^2. Kidney failure was defined as the first occurrence of either long-term kidney replacement therapy, a confirmed eGFR <15 mL/min/1.73m^2 or chronic kidney disease stage 5 recorded in RaDaR.[19]

eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; RASi, renin-angiotensin system inhibitor; UK, United Kingdom; yrs, years.

Patients with proteinuria ≥0.5 g/day and eGFR decline >1 mL/min/1.73m^2/year are at risk of progressive loss of kidney function[19,20]

eGFR and proteinuria are the only validated prognostic serum or urine biomarkers in IgA nephropathy.[20] Even among patients with lower levels of proteinuria (~0.5–<1.0 g/day,* n=175) , 31% progress to kidney failure within 10 years of diagnosis.†[19]

Kaplan-Meier survival curves of time to kidney failure/death by proteinuria level*†[19]



Adapted from Pitcher D, et al. Clin J Am Soc Nephrol. 2023.[19]

The KDIGO 2025 Guideline sets a proteinuria threshold of ≥0.5 g/day to consider:[20]

- **Kidney biopsy** in all adults in whom IgA nephropathy is a possible diagnosis‡
- **Treatment or additional treatment** in adults diagnosed with IgA nephropathy

The Guideline also recommends treatment goals of:[20]

- **Proteinuria** of at least <0.5 g/day and ideally <0.3 g/day
- **eGFR** decline of <1 mL/min/1.73m^2/year

Considering the underlying pathogenesis of IgA nephropathy may help reduce progression to kidney failure[1,20]

* UPCR cannot be directly compared with 24-hour proteinuria.[21] UACR values converted to UPCR using UPCR=UACR/0.7. A UPCR of 0.88 g/g may be considered comparable with protein excretion of 1 g/day.[19]

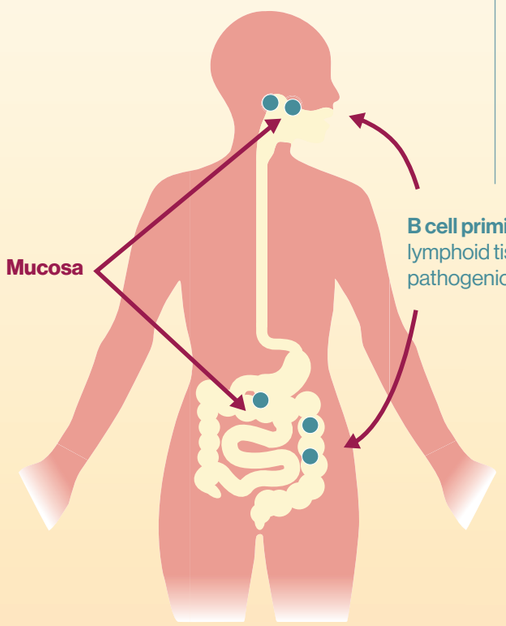
† Data from a retrospective cohort of the UK National Registry of Rare Kidney Diseases (RaDaR) (N=2439).[19] Kidney failure was defined as the first occurrence of either long-term kidney replacement therapy, a confirmed eGFR <15 mL/min/1.73m^2, or chronic kidney disease stage 5 recorded in RaDaR.[19]

‡ In whom kidney biopsy is not contraindicated.[20]

eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio; UK, United Kingdom; UPCR, urine protein-to-creatinine ratio.

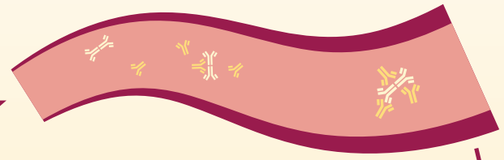
IgA nephropathy pathogenesis is underpinned by two fundamental, ongoing drivers of nephron loss, which are associated with multiple dysregulated pathways[1,22–24]

The IgA nephropathy-specific driver:[1,22–24]



Mucosa

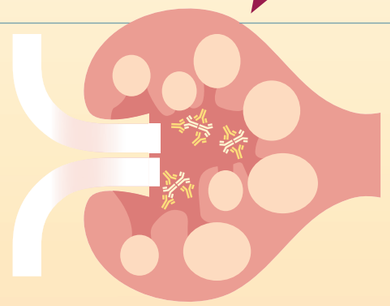
B cell priming in mucosa-associated lymphoid tissue triggers the multi-hit pathogenic process



Bloodstream

Increase of Gd-IgA1 in the systemic circulation leads to the formation of anti-Gd-IgA1 autoantibodies, which create immune complexes

Deposition of immune complexes in the glomerular mesangium leads to glomerular inflammation and injury, resulting in nephron loss



Mesangium

Glomerular inflammation

Glomerular hypertension, hyperfiltration, proteinuria and tubulointerstitial fibrosis

Maladaptive compensatory mechanisms lead to ongoing nephron loss, resulting in permanent kidney damage

The CKD driver:[1,23,24]

APRIL/BAFF signalling mediates production of Gd-IgA1, the initiating pathogenic event in IgA nephropathy[22]

The complement system is activated in response to mesangial deposition of immune complexes, contributing to glomerular inflammation[1,24]

A number of mechanisms are involved in the CKD driver of nephron loss.[20,24]

Endothelin pathway activation leads to mesangial cell activation, podocyte dysfunction, tubulointerstitial injury and glomerular hypertension*[24]

Other processes that drive inflammation and fibrosis in CKD include **RAS, SGLT2 and mineralocorticoid signalling**†[1,20]

The two fundamental drivers of nephron loss act via distinct mechanisms and should be considered simultaneously at diagnosis[1,20,22,24]

* Based on preclinical data from animal and cellular models.[24]

† Not an exhaustive list.

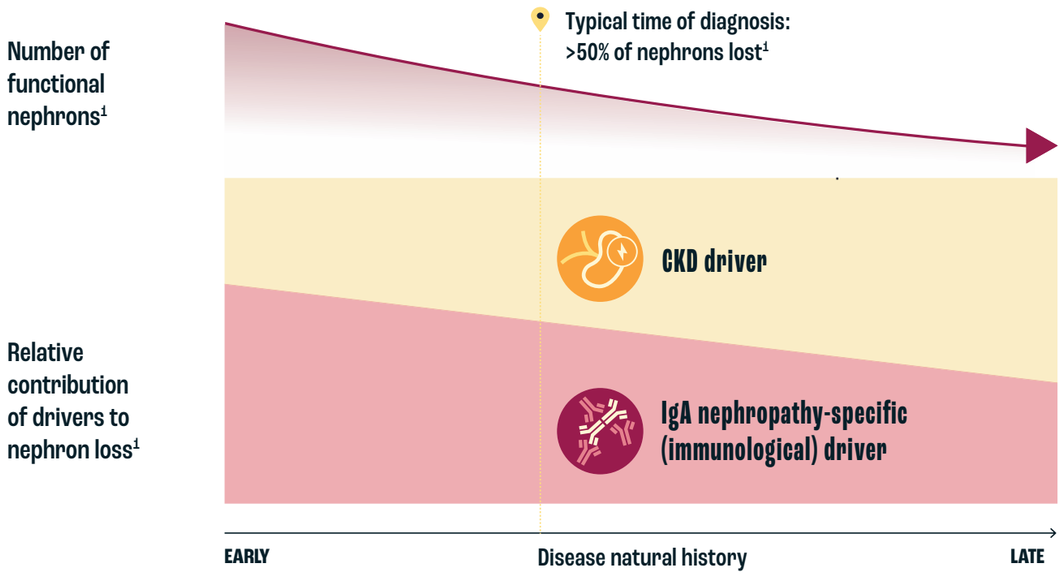
APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; CKD, chronic kidney disease; Gd-IgA1, galactose-deficient immunoglobulin A1; IgA, immunoglobulin A; RAS, renin-angiotensin system; SGLT2, sodium-glucose co-transporter 2.

Both fundamental drivers mediate ongoing nephron loss from the time of diagnosis[1]

During the initial stages of disease, often prior to diagnosis, the IgA nephropathy-specific driver is the greater contributor to nephron loss.[1]

However, as continual nephron loss occurs, the CKD driver becomes a greater contributor to disease progression.[1]

Given patients may have lost >50% of nephrons at the typical time of diagnosis and no nephron lost can be regained, it is essential to consider both fundamental drivers of nephron loss from diagnosis.[1,23]



Adapted from Barratt J, et al. Front Med. 2024.[1] Stylised representation for illustrative purposes.

Pathogenic mechanisms behind the two fundamental drivers of nephron loss should be considered when treating IgA nephropathy[1,20]

CKD, chronic kidney disease; IgA, immunoglobulin A.

The KDIGO 2025 Guideline recommends a multifaceted approach that considers the two fundamental drivers of nephron loss simultaneously from diagnosis[20]

Management of IgA nephropathy should consider the underlying pathogenic mechanisms of the disease, with an aim of reducing further nephron loss and slowing kidney function decline[1,20]

IgA nephropathy-specific driver considerations[20]

- Synthesis of pathogenic IgA
- IgA immune complex formation
- IgA and IgA immune complex-mediated kidney injury

CKD driver considerations[20]

- Glomerular hyperfiltration
- Proteinuria and the impact of proteinuria on the tubulointerstitium
- Elevated blood pressure

The KDIGO 2025 Guideline calls for a tailored treatment paradigm targeting the underlying pathogenesis of IgA nephropathy to help preserve kidney function for as long as possible[20]

CKD, chronic kidney disease; IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes.

Tune into change: With an improved understanding of IgA nephropathy pathogenesis comes the opportunity to embrace a new treatment paradigm[1,18,20,23]

Patients with IgA nephropathy and proteinuria of ≥0.5 g/day are at risk of progression to kidney failure[19,20]

The KDIGO 2025 Guideline recommends a multifaceted approach that considers the two fundamental drivers of nephron loss simultaneously from diagnosis[20]

IgA nephropathy pathogenesis is underpinned by two fundamental drivers of nephron loss involving multiple pathways[1,20,22,24]

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IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes.

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