Advancing Therapeutic Goals in IgA Nephropathy

IgA Nephropathy (IgAN)

Epidemiology

IgAN is the most prevalent primary glomerulonephritis worldwide[1]

2.5/100,000 people are affected per year[2]

30–40% of all primary glomerular disease in Europe is IgAN[1]

Burden

IgAN is a leading cause of CKD and kidney failure[3]

up to 53% of patients develop kidney failure within 20 years of diagnosis[4]

Patients are often diagnosed late-stage with symptoms of established kidney disease, including proteinuria, renal insufficiency, haematuria, and hypertension.[5]

Management

Initial supportive care including lifestyle modification (e.g., weight reduction, increased physical activity, and dietary sodium restriction), blood pressure control and maximum tolerated RAS blockade when proteinuira **>0.5 g/d**.[3]

Unmet need

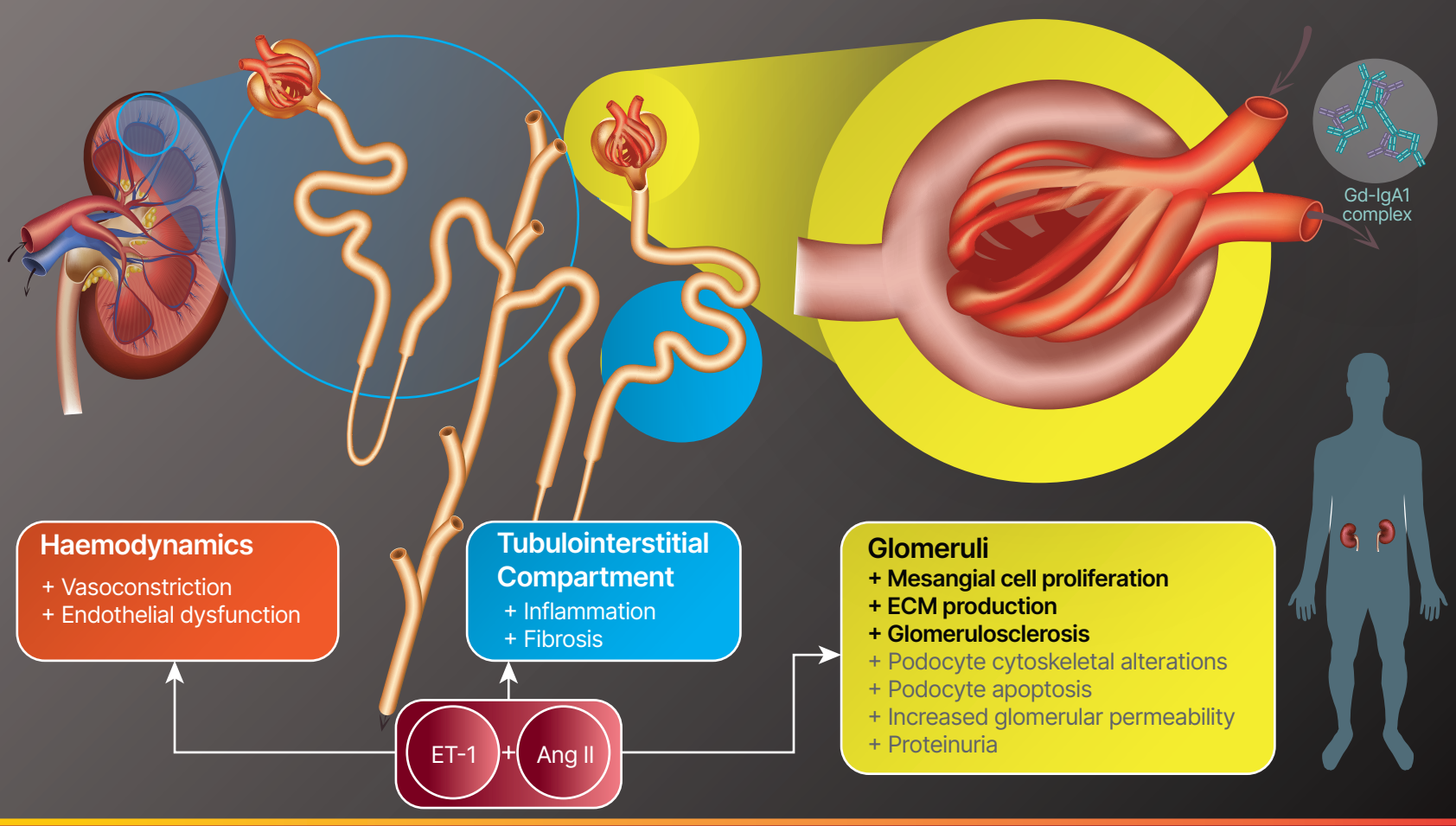
64%

of patients remain above proteinuria targets when treated with current first-line therapies ACEis and ARBs[6]

Pathophysiology

IgAN is characterised by the mesangial deposition of galactose-deficient immunoglobulin A1 (IgA1) immune complexes, which stimulates mesangial cell activation and proliferation, increases production of inflammatory cytokines and mediators, including ET-1 and Ang II, and stimulates expansion of extracellular matrix (ECM) components.[7–9]

ET-1 and Ang II act in tandem to amplify inflammation and damage to the glomerular filtration barrier and tubulointerstitial compartment and cause vascular dysfunction, leading to increased proteinuria, a progressive loss of glomerular filtration rate ultimately leading to kidney failure.[10-12]



Therapeutic Goals in IgAN

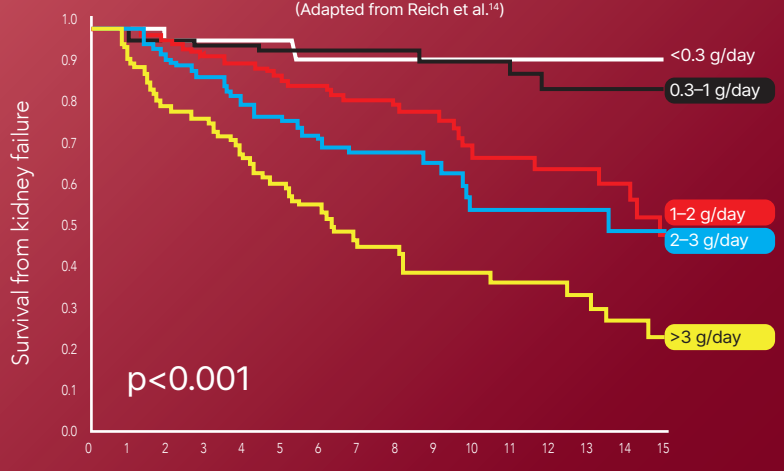
Managing blood pressure and proteinuria thus slowing the progression to kidney failure[3]

<1 g/day proteinuria

<120 mmHg systolic blood pressure [3,13]

Proteinuria is the single strongest and modifiable prognostic factor in IgAN,with sustained levels >1 g/day associated with a faster rate of kidney function decline[14]

(Adapted from Reich et al.[14])



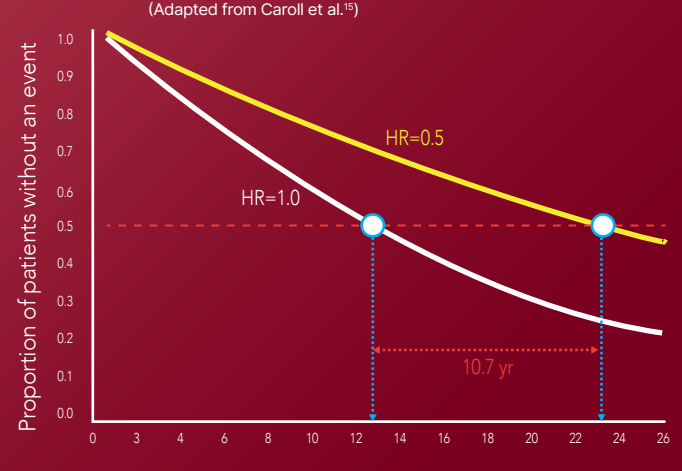
Hypothesised treatment effect on proteinuria estimated that a 30% reduction in proteinuria at 9 months conferred a 50% lower risk of ESKD, extending the median time to ESKD by 10.7 years[15]

(Adapted from Caroll et al.[15])

HR
HR=1.0 represents no treatment effect on proteinuria from baseline: Median time to event 12.4 yr, 90% CI (15.9, 33.5)

HR
HR=0.5 represents 30% treatment effect on proteinuria from baseline: Median time to event 23.1 yr, 90% CI (13.5, 28.5)

Ratio of medians 1.86, 90% CI (1.55, 2.24)



ACEis: angiotensin-converting enzyme inhibitors; Ang II: angiotensin II; ARBs: angiotensin receptor blockers; CI: confidence interval; CKD: chronic kidney disease; ECM: extracellular matrix; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; ESRD: end-stage renal disease; ET-1: endothelin-1; Galactose-deficient immunoglobulin A1 (Gd-IgA1) HR: hazard ratio; RAS: renin-angiotensin system; Yr: year

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References

1. Kidney Disease: Improving Global Outcomes (KDIGO). Chapter 10: Immunoglobulin A nephropathy. Kidney Int Suppl (2011). 2012;2(2):209–217.
2. McGrogan A et al. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011;26(2):414-430.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1–S276.
4. Hastings MC et al. Life expectancy for patients from the South-eastern United States with IgA nephropathy. Kidney Int Rep. 2017;3(1):99–104.
5. Lafayette RA, Kelepouris A. Immunoglobulin A nephropathy: advances in understanding of pathogenesis and treatment. Am J Nephrol. 2018;47(Suppl 1):43-52.
6. Bagchi S et al. Supportive management of IgA nephropathy with renin-angiotensin blockade, the AIIMS primary IgA nephropathy cohort (APPROACH) study. Kidney Int Rep. 2021;6(6):1661-8.
7. Suzuki H et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22(10):1795-803.
8. Lai KN et al. IgA nephropathy. Nat Rev Dis Primers. 2016;2:16001.
9. Wyatt RJ, Julian BA . IgA nephropathy. N Engl J Med. 2013;368(25):2402-14.
10. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. Kidney Int. 2014;86(5):896-904.
11. Komers R, Plotkin H. Dual inhibition of renin-angiotensin-aldosterone system and endothelin-1 in treatment of chronic kidney disease. Am J Physiol Regul Integr Comp Physiol. 2016;310(10):R877-84.
12. Raina et al. The Role of Endothelin and Endothelin Antagonists in Chronic Kidney Disease. Kidney Dis (Basel). 2020;6(1):22-34.
13. Cheung A et al. Executive summary of the KDIGO 2021 clinical practice guidelines for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(3):559-69.
14. Reich HN et al.; Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18(12):3177-83.
15. Carroll KJ et al. Estimating Delay in Time to ESKD for Treatment Effects on Proteinuria in IgA Nephropathy and FSGS. Oral Presentation MO246. ERA-EDTA. 2021.

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