Advancing Therapeutic Goals in IgA Nephropathy

IgA Nephropathy (IgAN)

Epidemiology

IgAN is the most prevalent primary glomerulonephritis worldwide[1]

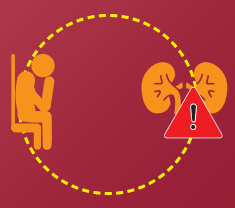
2.5/100,000 people are affected per year[2]

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 insuffi-ciency, 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]

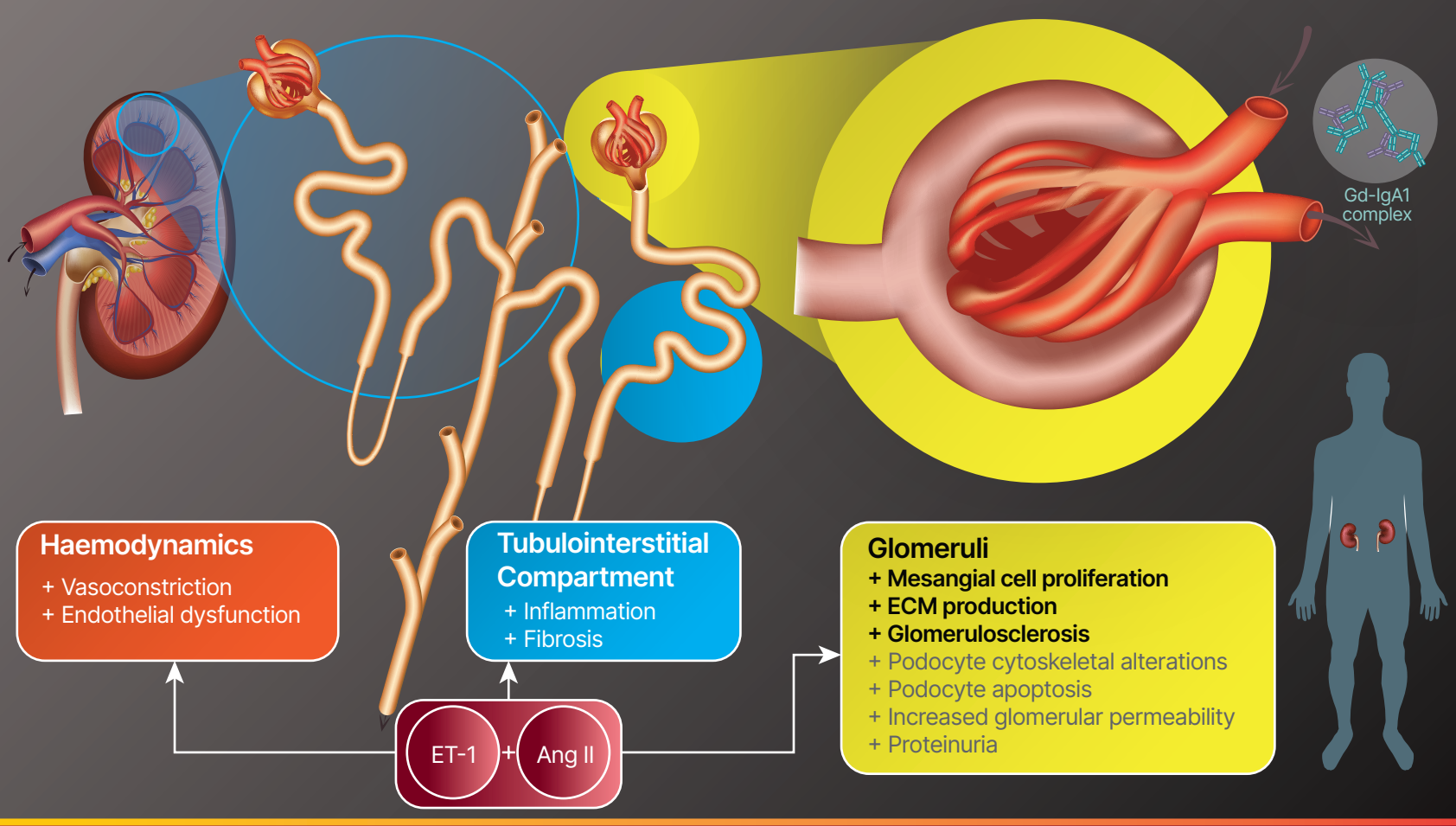
Unmet need

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

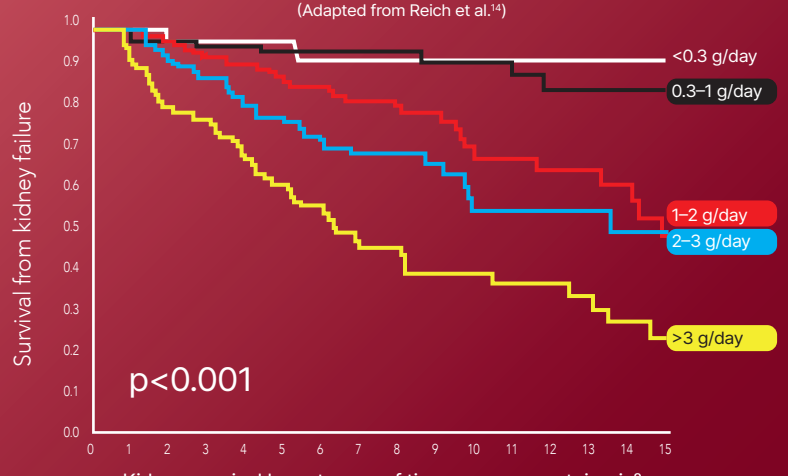
Managing blood pressure and proteinuria thus slowing the progression to kidney failure[3]

<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])



Kidney survival by catagory of time-average proteinuria[9]

Years

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])

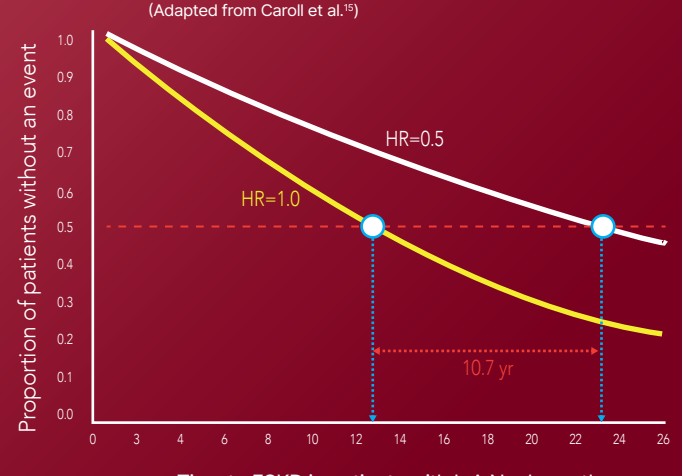
HR

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)



Time to ESKD in patients with IgA Nephropathy

Time to ESRD or time to eGFR <15 ml/min/1.73 m² (years)

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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