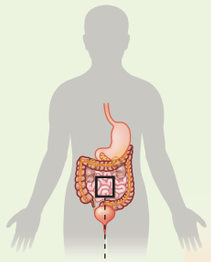
KDIGO FOCUS
IgA Nephropathy

- IgA nephropathy is the most common glomerular disease worldwide. As many as 15–20% of affected patients progress to kidney failure in 10 years and 30–40% of patients do so in 20 years.
- Prevalence for IgA nephropathy has been reported to be >2.5 cases per 100,000 in Europe and North America, though the highest rates have been observed in the Asian Pacific region and the lowest in Africa.
- Average age of diagnosis for IgA nephropathy is around 40 years, which is during prime years of productivity. Even patients traditionally considered as low risk with < 1 g/d of proteinuria have a high probability (30%) of kidney failure within 10 years.
- IgA nephropathy poses a significant burden on quality of life. In one survey, almost half the adults reported depression and close to a third reported work impairment as a result. Their care partners are not immune to the influence of the disease as they experienced mental and physical deficits in their quality of life as well.
- Traditionally, treatments for IgA nephropathy focus on managing the consequences of the disease (e.g., RASi for proteinuria reduction). However, our enhanced understanding of the pathomechanisms now allows the direct targeting at the drivers of disease, potentially enabling more effective treatments.

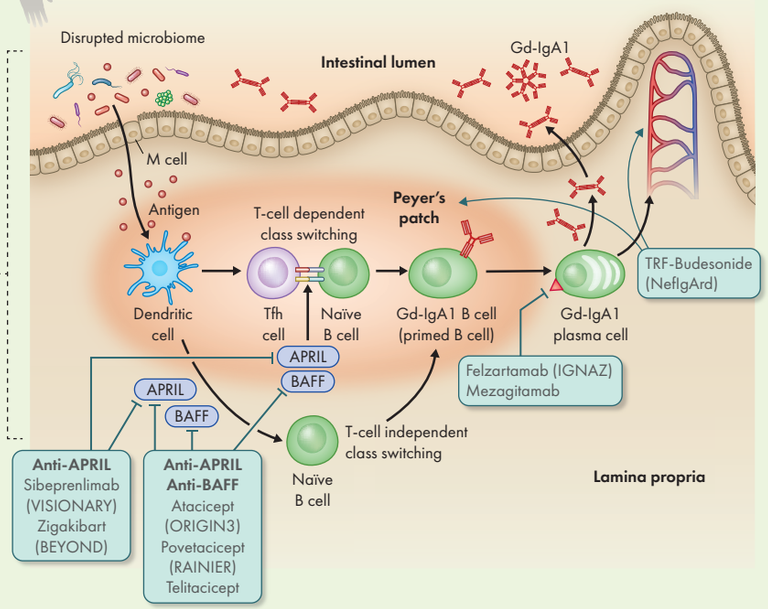
Sources: Appel GB. Glomerulonephritis, p. 367, 2019; Stamellou et al. Nat Rev Disease Primer, p. 67, 2023; Pitcher D et al. CJASN, p. 727, 2023; Szklarzewicz J et al. Quality of Life Research https://doi.org/10.1007/s11136-024-03813-x, 2024

SNAPSHOT OF IgA NEPHROPATHY PATHOPHYSIOLOGY
MECHANISTIC TARGETS OF POTENTIAL NOVEL THERAPIES

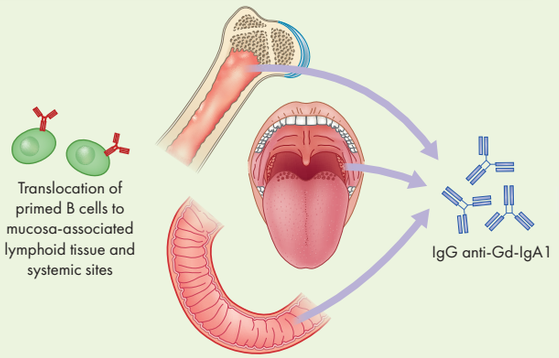
The pathogenesis of IgA nephropathy (IgAN) is illustrated by the current "4-hit hypothesis" which involves four sequential processes that must occur before IgAN disease develops. Our improved understanding of IgAN pathophysiology has allowed the identification of potential therapeutic agents targeting these requisite steps. It is envisioned that such targeted treatments will be used alongside existing therapies (e.g., RASi, SGLT2i, dual ERA) that slow progressive CKD in injured kidneys. These promising agents will be selected and personalized based on the patient's individual risk profile (e.g., risk factors, disease severity, treatment response). Agents targeting specific disease pathways are denoted below with the latest trial acronym in parentheses.



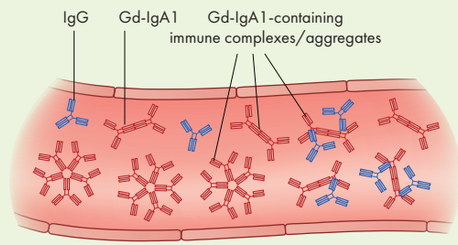
HIT 1: Production of pathogenic forms of IgA1, commonly measured as galactose-deficient IgA1 (Gd-IgA1)



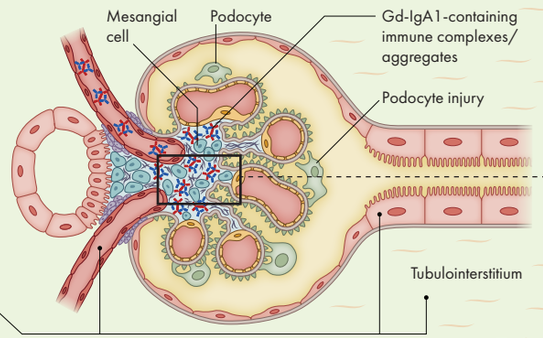
HIT 2: Generation of IgG/IgA autoantibodies against Gd-IgA1



HIT 3: Formation of GD-IgA1 and anti-GD-IgA1 immune complexes and/or GD-IgA1 immune aggregates

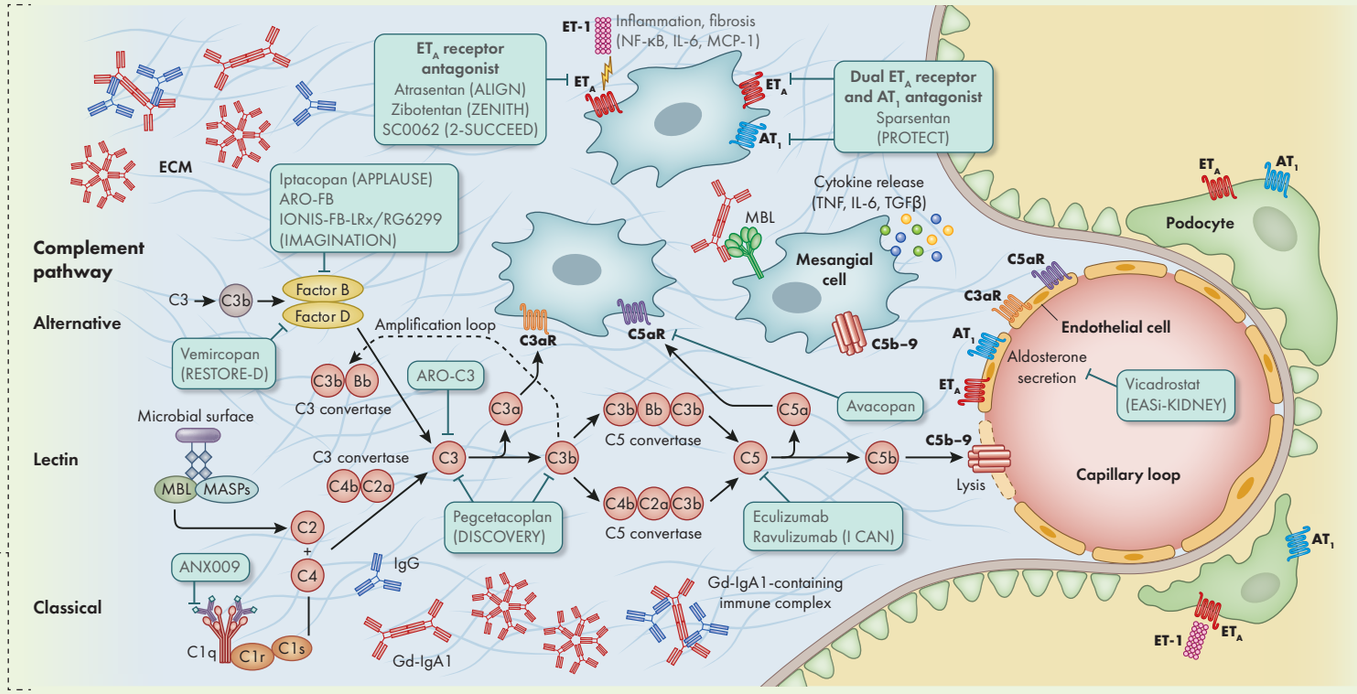


HIT 4: Deposition of Gd-IgA1-containing immune complexes/aggregates in the mesangium leading to inflammation, fibrosis and podocyte injury



- Endothelial receptor antagonists
- SGLT2i
- RASi

exert beneficial hemodynamic effects on glomerular vasculature and direct effects on multiple kidney parenchymal cell types to attenuate inflammation, fibrosis and proliferation



APRIL, A proliferation-inducing ligand; AT1, angiotensin type 1; BAFF, B-cell–activating factor; C3aR, C3a receptor; C5aR, C5a receptor; ECM, extracellular matrix; ERA, endothelin receptor antagonist; ET-1, endothelin 1; ETA, endothelin A; IL-6, interleukin 6; MASP, MBL-associated serine proteases; MBL, mannose-binding lectin; MCP-1, monocyte chemoattractant protein-1; NF-κB; nuclear factor-κB; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TGF-β, transforming growth factor β; TNF, tumour necrosis factor; TRF, targeted release formulation

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