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Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and carries a substantial risk of kidney failure. New agency-approved therapies, either specifically for IgAN or for chronic kidney disease (CKD) in general, hold out hope for mitigating renal deterioration in patients with IgAN. The latest addition to this therapeutic armamentarium targets the endothelin-A receptor (ET_AR). Activation of ET_AR on multiple renal cell types elicits a host of pathophysiological effects, including vasoconstriction, cell proliferation, inflammation, apoptosis, and fibrosis. Blockade of ET_AR is renoprotective in experimental models of IgAN and reduces proteinuria in patients with IgAN. This review discusses the evidence supporting the use of ET_AR blockade in IgAN as well as addressing the potential role for this class of agents among the current and emerging therapies for treating this disorder.

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Since its original description over 5 decades ago, IgAN has become recognized as the most common primary glomerulonephritis worldwide. It is characterized by the presence of dominant or codominant mesangial IgA deposits on immunostaining of kidney biopsy tissue.[1] The true disease prevalence is unknown because practices of screening for asymptomatic renal disease and access to care (including biopsies) vary widely across the world. Notwithstanding these caveats, the incidence of IgAN is highest in East Asia followed by Europe and North America, accounting for about 45%, 25%, and 12% of native kidney biopsies, respectively, and is very rare in Central Africa.[2] The pathologic features are also heterogeneous with inflammatory lesions, including endocapillary hypercellularity and crescents, reported more in Asian than European cohorts. This pathologic variability also mirrors a more severe clinical phenotype among Asians and a higher risk of disease progression.[3,4] A recent study from the United Kingdom Rare Disease Registry, which includes over 4000 patients with IgAN, reported that based on estimated glomerular filtration rate (eGFR) and age at diagnosis, almost all patients with IgAN are at risk of progression to kidney failure within their expected lifetime unless a yearly rate of eGFR loss <1 ml/min per 1.73 m^2 can be maintained.[5]

Three therapies have recently been added to the clinical armamentarium for treating IgAN: gut-targeted steroids, sodium-glucose cotransporter-2 inhibitors (SGLT2i), and most recently, a dual ET_AR and angiotensin II (AngII) receptor antagonist. Each of these new agents have different biological targets and may prove to be most effective when given in some combination. Although several recent reviews have discussed the use of gut-targeted steroids in IgAN and SGLT2i in CKD, none have focused on the role of the endothelin (ET)/ET_AR system in IgAN; the current review addresses this knowledge gap.

Pathogenesis of IgAN

The pathogenesis of IgAN is influenced by genetic and environmental factors and is thought to involve 4 hits. Elevated levels of mucosal and circulating galactose-deficient IgA1 (Gd-IgA1) (hit 1) are recognized by IgG or IgA1 autoantibodies (hit 2). Pathogenic Gd-IgA1–auto-Ab immune complexes (IC) form (hit 3) that are deposited in the mesangium, causing glomerular injury (hit 4).[6]

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Mucosal IgA production by plasma cells occurs by T cell-dependent and T cell-independent processes. T cell cytokines such as a proliferation-inducing ligand (APRIL) promote B cell class switch to IgA1-producing plasma cells.[7] The mechanisms underlying production of Gd-IgA1 are unclear, but susceptibility to sporadic and familial IgAN are linked to variants in multiple loci involving major histocompatibility complex (MHC) and non-MHC susceptibility alleles.[8-10] Further evidence of genetic underpinnings to aberrant Gd-IgA1 production include the fact that 40% to 50% of first-degree relatives of patients with IgAN have similarly elevated Gd-IgA1 levels.[11]

Mucosal infections may contribute to the development of IgA1 and IgG autoantibodies to Gd-IgA1. Gross hematuria is often observed with mucosal infections in patients with IgAN, and antigens for pathogens including *Staphylococcus aureus*, *Haemophilus parainfluenzae*, and cytomegalovirus have been identified in IgAN patient glomeruli.[12-14] It has been postulated that antibodies produced in response to commensal or infectious microorganisms cross-react with galactose-deficient *O*-linked glycans on IgA1.[6] Indeed, a recent study demonstrated more tonsil *Neisseria* as well as elevated *Neisseria*-targeted serum IgA in IgAN compared with controls.[15] This study also identified anti-*Neisseria*-specific IgA-secreting cells within kidneys in a B cell-activating factor of the TNF family transgenic rodent IgAN model. Taken together, these findings suggest that in genetically susceptible individuals, cytokine-driven aberrant mucosal immune responses promote the development of IgA-dominant disease.

Complement activation, particularly through the alternative pathway, is an important contributor to the pathogenesis of IgAN. Proteomic analyses of IgAN patient circulating IC and complexes formed *in vitro* from Gd-IgA1 and antiglycan IgG revealed the presence of C3.[16] C3 mesangial immune codeposition with properdin and complement factor H is a hallmark of IgAN.[16] Polymeric IgA can also activate the lectin pathway which is an important pathogenic IgAN contributor.[17] Mannose binding lectin is codeposited with IgA in 17% to 25% of IgAN biopsies with mannose binding lectin codeposits correlating with severity of the disease.[18,19]

Though receptors involved in IgA1-IC binding are poorly defined, the glomerular mesangium, located between the fenestrated endothelial capillary lining and glomerular basement membrane, is uniquely susceptible to IC deposition.[6] Immune complex deposition results in a glomerular injury cascade amplified by local alternative and lectin complement pathway activation that involves mesangial cells (MCs), podocytes, the vasculature, and tubular epithelial cells.[20] The renal injury induced by IC and complement activates multiple factors that mediate vasoconstriction, cell proliferation, podocyte effacement, glomerulosclerosis, and tubulointerstitial damage. As will be described, the ET/ET_AR system plays an important role in this injury process.

Physiology and Pathophysiology of Endothelin in the Kidney

Basic Biology and Pathology of Endothelin in the Kidney

Endothelin-1 (ET-1) is a 21-amino acid peptide that was originally described 35 years ago as an endothelial-derived vasoconstrictor.[21] It is now evident that ET-1 is produced by and acts upon multiple cell types within most organs to elicit a plethora of biological responses. There are 3 ET peptides (ET-1, ET-2, and ET-3) and 2 ET receptors (ET_AR and ET_BR). The ET_AR preferentially binds ET-1 and ET-2, whereas the ET_BR binds all 3 peptides with equal affinity. The ET_AR and ET_BR were originally described to cause vasoconstriction and vasodilation, respectively; however, these receptors mediate a wide variety of actions which can be complementary or opposing.

The kidney is a major organ source of ET-1. This review focuses on ET-1 because it is the primary peptide involved in kidney physiology and pathophysiology.[22] Virtually every renal cell type makes ET-1 and expresses ET receptors; therefore, the peptide acts primarily in an autocrine and/or paracrine manner. Renal ET-1 production is stimulated by many factors, including vasoactive, proliferative, fibrotic, inflammatory, oxidative, metabolic, and others.[23,24] Urinary ET-1 excretion, which solely reflects renal ET-1 production, is elevated in virtually all kidney diseases in which it has been examined.[23]

ET-1 regulates multiple renal physiological functions, including vascular tone, tubular epithelial cell ion (e.g., sodium, chloride, hydrogen, and bicarbonate) and water transport, juxtaglomerular apparatus renin secretion, MC contraction, and others.[22] In general, renal ET-1 is particularly important in maintaining blood pressure and fluid and electrolyte homeostasis.[22]

Activation of ET_AR induces a broad spectrum of pathophysiologic effects, including platelet aggregation and adhesion, immune cell migration and cytokine production, MC and vascular smooth muscle contraction, podocyte effacement and proteinuria, cell proliferation and migration, extracellular matrix accumulation and fibrosis, induction of other proinjurious factors (e.g., AngII and aldosterone), and others (Figure 1).[23,24] Some of these factors contribute to positive feedback by further promoting ET-1 synthesis,

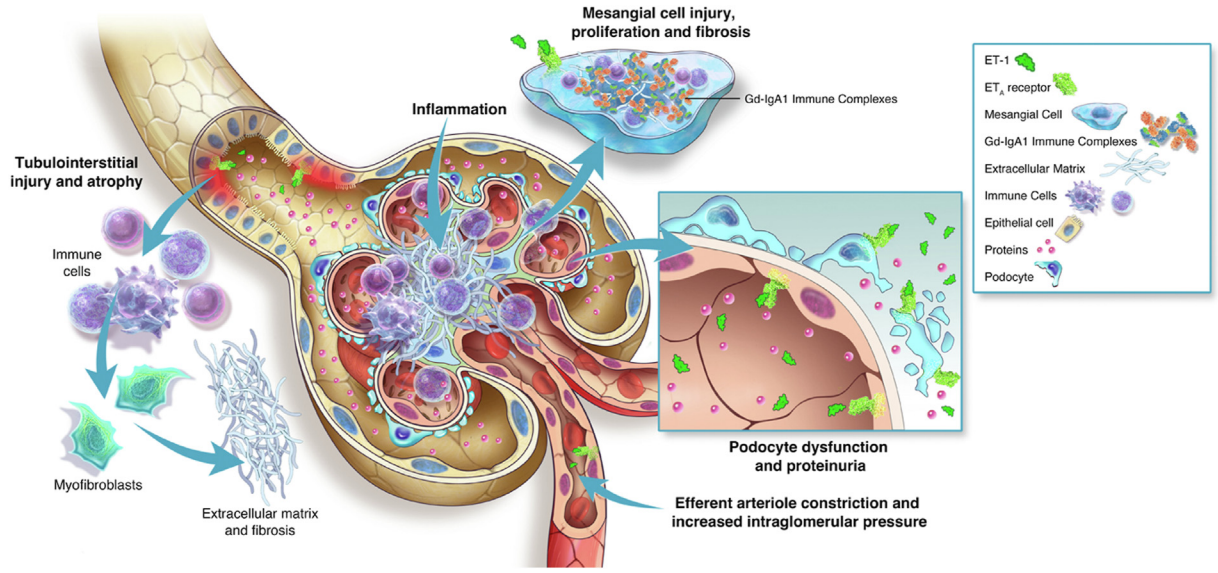

Figure 1. Mechanisms of endothelin-1 (ET-1)/ET$_A$ receptor mediated renal injury in IgA nephropathy.

including AngII and proteinuria.[23,25] In contrast, the renal ET$_B$R is vasodilatory (via nitric oxide and prostacyclin release) and clears ET-1 from the extracellular space; therefore, inhibiting ET$_B$R would not be expected to improve renal injury. Indeed, numerous studies examining ET receptor antagonism in multiple experimental forms of acute and CKD have found that ET$_A$R blockade almost uniformly improves outcomes, whereas combined ET$_A$R/ ET$_B$R inhibition often has no effect or worsens outcomes.[23,24]

Renal Vasculature and Endothelin

Studies on the ET system in the renal vasculature have sometimes led to confusion due, at least partly, to differences between species and experimental models. However, most data point to a substantial role for ET$_A$R, particularly in the efferent arteriole, in promoting renal injury.

Both ET$_A$R and ET$_B$R are expressed throughout the renal vasculature in humans and experimental animals, with ET$_A$R predominating in vascular smooth muscle and ET$_B$R predominating in the endothelium.[26,27] The ratio of ET$_A$R to ET$_B$R in human renal artery is approximately 90:10 and approximately 92:8 in renal vein.[28] Systemically or intrarenally administered ET-1 causes marked whole kidney vasoconstriction.[22] The direct effects of ET-1 on the renal microvasculature have been determined *in vitro*. In isolated rat and rabbit arterioles, ET-1 elicited potent and long-lasting constriction with efferent arteriole up to 10-fold more sensitive than afferent arteriole.[29-31] In contrast, studies using hydronephrotic kidney, isolated perfused kidney, or blood-perfused juxtamedullary nephron rat models found that ET-1 more potently constricted afferent than efferent arterioles.[22] Unfortunately, rat kidney is not ideal to examine this issue since both ET$_A$R and ET$_B$R can be vasoconstrictive, whereas only ET$_A$R constrict the renal vasculature in dogs, rabbits, and humans.[32] In canine kidney micropuncture studies, ET-1 reduced renal blood flow and GFR via ET$_A$R, increasing afferent and efferent arteriolar resistance and decreasing ultrafiltration coefficient, pointing to greater ET-1 efferent than afferent arteriole actions.[33]

Blockade of ET$_A$R in healthy humans and conscious animals modestly reduces systemic arterial pressure but does not detectably alter renal hemodynamics.[33-37] In contrast, ET$_B$R antagonism produced marked systemic and renal vasoconstriction in healthy humans.[35] Therefore, in healthy individuals, ET$_A$R does not contribute significantly to renal vascular tone, whereas ET$_B$R maintains vasodilation. In contrast, a vasoconstrictive effect of ET$_A$R is uncovered in healthy humans if either an angiotensin converting enzyme inhibitor (ACEi) or AngII type 1 receptor blocker are administered. In 2 studies, a short-acting ET$_A$R antagonist (BQ123) was given to 6 healthy subjects before and after renin-angiotensin system (RAS) blockade; BQ123 increased renal blood flow and reduced filtration fraction only after RAS blockade.[34,36] These findings support the notion that in healthy individuals, efferent arteriolar ET$_A$R can interact with the RAS to modulate renal blood flow.

The role of ET$_A$R in modulating renal hemodynamics is most evident in individuals with CKD (almost all of whom are taking RAS inhibitors). Acute ET$_A$R blockade increased renal blood flow and reduced filtration fraction whereas only modestly decreasing arterial pressure in 2 studies with a combined total of 30 subjects with CKD (13 with IgAN).[35,38] In contrast,

acute ET_BR blockade produced substantial renal vasoconstriction and prevented the renal hemodynamics effects of ET_AR blockade. In addition, 6 weeks of treatment with sitaxsentan, an ET_AR antagonist, reduced proteinuria, GFR, and filtration fraction in 13 CKD subjects.[39] Taken together, these studies suggest that selective ET_AR blockade, primarily via actions in the efferent arteriole, exerts beneficial effects on renal hemodynamics in CKD, particularly in the context of RAS inhibition.

The Glomerulus and Endothelin

MCs. The pathophysiological effects of ET-1 on MC are largely mediated by ET_AR.[23,32] These actions include stimulation of proliferation, contraction, and extracellular matrix accumulation. Numerous agents augment MC ET-1 production, including growth, vasoactive (e.g., AngII), fibrotic, inflammatory, and proliferative factors.[40] ET-1, through autocrine or paracrine (i.e., ET-1 derived from endothelial cells, MC, or podocytes) mechanisms, activates a host of well-characterized intracellular signaling mechanisms in MC that elicit sustained pathophysiologic effects.[32] Importantly, ET-1 can be involved in pathological positive feedback pathways that facilitate continued glomerular injury. For example, tumor necrosis factor, interleukin-1, and transforming growth factor-ß enhance MC ET-1 production, which in turn augments MC and neighboring cell production of all these factors.[40] In addition, ET-1 increases MC collagen accumulation through an autocrine loop involving interleukin-6 and macrophage chemoattractant protein-1.[41] Finally, ET-1-stimulated MC fibronectin synthesis is reduced by losartan, whereas AngII-stimulated fibronectin is decreased by ET_AR blockade.[42] As will be described later in this review, ET-1 and MC are likely of particular importance in the pathophysiology of IgAN.

Podocytes. The ET-1/ ET_AR axis also plays an important role in podocyte injury. AngII, proteinuria, and other factors enhance podocyte ET-1 synthesis, which can then act in an autocrine or paracrine manner.[32,43,44] Activation of podocyte ET_AR promotes actin cytoskeleton disassembly, slit diaphragm dysfunction, nephron shedding, apoptosis, and podocyte depletion, as well as stimulating inflammation and fibrosis.[32] Many of the studies on the ET system and podocytes have focused on experimental models of focal segmental glomerulosclerosis and diabetic kidney disease wherein ET_AR blockade is protective.[32,43,45] However, as will be described in the following section, ET-1/ ET_AR are also involved in podocyte injury in IgAN.

Glomerular Endothelium. Endothelial cells are likely the major source of ET-1 in normal human kidney.[46] Crosstalk between endothelial cells and podocytes is involved in glomerular injury. In a model of focal segmental glomerulosclerosis, endothelial dysfunction, via mitochondrial oxidative stress, promoted podocyte apoptosis and this was abrogated by inhibition of ET_AR.[43] In this same model, endothelial glycocalyx degradation was associated with ET-1-stimulated heparanase and was prevented by ET_AR, but not ET_BR, blockade.[47] In a diabetic CKD model, ET-1 induced podocyte heparanase release, whereas podocyte-specific knockout of both ET receptor subtypes prevented glycocalyx loss (as well as proteinuria and renal failure).[48] Taken together, it is likely that a complex interaction between endothelial cells, MC, and podocytes exists in which ET-1/ ET_AR together with other factors promote glomerular injury.

The Renal Tubule and Endothelin

ET-1 is an important regulator of renal tubule function in health and disease. The renal tubule primarily expresses ET_BR although ET_AR are present.[49] Most tubule segments synthesize ET-1; the collecting duct, particularly in the inner medulla, produces more ET-1 than any other known cell type.[49] ET-1, mainly via ET_BR, inhibits collecting duct epithelial Na^+ channel, thick ascending limb $Na^+/K^+/2Cl^-$ cotransporter, and proximal tubule Na^+/H^+ exchanger-3 mediated sodium reabsorption.[22] The collecting duct ET_AR is functionally important in that collecting duct-specific ET_AR knockout prevents ET_AR antagonist-induced fluid retention; this effect may account, at least partly, for ET_AR blocker-induced fluid retention observed clinically.[50]

Renal tubular cells may also contribute to ET-1-induced renal injury. Exposure of cultured proximal tubule cells to albumin increases ET-1 synthesis.[51,52] In a model of membranous nephropathy with substantial proteinuria, proximal tubule and interstitial ET-1 mRNA were upregulated to a much greater extent than elsewhere in the kidney.[53] Such tubule-derived ET-1 could promote tubulointerstitial fibrosis.[54] Therefore, proteinuria and proximal tubule-derived ET-1 may act via a positive feedback loop to cause renal damage.

Interaction Between the Endothelin and Renal-Angiotensin Systems

The interaction between ET-1 and AngII is important in renal disease. These 2 peptides induce similar pathophysiological processes through different, albeit complementary, signaling processes. For example, in vascular smooth muscle cells, AngII elicits a rapid mobilization of calcium from intracellular stores via inositol phosphate-3, whereas ET-1 causes sustained increases in intracellular calcium primarily by stimulating cellular influx through calcium channels.[55]

Similarly, AngII elicits more rapid vascular smooth muscle contraction, whereas ET-1 effects are more sustained; similar kinetics of ET-1 and AngII extracellular-regulated kinase activation occur.[55]

As described above, ET-1 and AngII stimulate one another's production, whereas inhibition of ET_AR or AT1 receptors reduces the other's pathophysiological effects. Several, albeit not all, studies found that combined ET_AR and AT1 receptor inhibition in CKD confers beneficial effects beyond those seen with either agent alone.[25] In addition to the enhanced hemodynamic effects of ET_AR blockade seen in the presence of RAS inhibition,[35,38] acute ET_AR inhibition reduced proteinuria more in CKD patients taking both AT1 receptor blockers and ACEi compared to ACEi alone.[56] In animals with experimental membranous nephropathy, combined ACEi and ET_AR blockade decreased proteinuria and glomerulosclerosis whereas neither agent alone had a significant effect.[57] In an experimental model of diabetic nephropathy, the combination of ACEi and avosentan (a predominantly ET_AR blocker) abolished proteinuria and induced regression of glomerular lesions, whereas single therapy was significantly less renoprotective.[58] Finally, as will be described in the ensuing clinical discussion, combined RAS inhibition and ET_AR blockade reduces proteinuria to a significantly greater extent than RAS inhibitors alone in patients with IgAN.[59,60] Taken together, these findings support the rationale for combined RAS inhibition and ET_AR blockade in CKD.

Pathophysiology of Endothelin in IgAN

Endothelin Pathway Activation in Human and Experimental IgAN

ET pathway activation was observed in kidney biopsies from patients with IgAN and appears to be associated with poor clinical outcomes. Elevated kidney ET-1 mRNA expression strongly and prospectively predicted clinical progression of IgAN 12 months following kidney biopsy.[61] Intense ET-1 and increased ET_AR immunostaining occurs in the glomeruli and the tubulointerstitial compartment in biopsies of patients with IgAN with significant proteinuria,[62,63] whereas renal ET-1 expression was generally low in biopsies from healthy controls and in patients with IgAN without significant proteinuria.[61] An intrarenal transcriptional signature of ET_AR activation has been used to quantify ET pathway activity in molecular profiles generated from kidney biopsies in patients with IgAN from the European Renal cDNA Bank cohort[64]; intrarenal ET_AR activation scores were significantly associated with clinical progression in patients with IgAN, including increased proteinuria and decreased eGFR. Unbiased serum proteomic analysis in the IgAN cohort from the NURTuRE CKD biobank revealed that serum ET-1 concentration was strongly associated with eGFR loss.[65]

Intrarenal ET pathway activation has also been observed in the ddY mouse, a spontaneous model of IgAN characterized by intense glomerular deposition of IgA, IgG, and complement C3.[66] Kidney expression of ET-1 and ET_AR progressively increased and were associated with increased urinary protein excretion, blood pressure, glomerular cell number, and decreased GFR. Therefore, ET pathway upregulation has been consistently observed in human and experimental progressive IgAN.

ET_AR Inhibition in Experimental IgAN

MC activation by IgA-containing IC is the initiating intrarenal event in the pathogenesis of IgAN and is characterized by cellular proliferation and overproduction of extracellular matrix, inflammatory cytokines, and chemokines (Figure 1). Subsequent MC-podocyte crosstalk promotes proteinuria, the strongest predictor of disease progression. The molecular mechanisms responsible for IC-mediated MC activation have not been well defined, although a potentially important role of ET_AR is emerging. The selective ET_AR antagonist, atrasentan, inhibited excess proliferation and interleukin-6 production in cultured human MCs in response to ET-1, and largely reversed ET-1-stimulated upregulation of proproliferative, proinflammatory and profibrotic gene pathways.[67] An important transcriptional target gene of exogenous ET-1 in human MCs was *Edn1* (ET-1), suggesting an autocrine signaling loop to amplify ET-1-mediated MC responses. Atrasentan also attenuated cultured human MC hyperproliferation in response to IgA-containing IC purified from IgAN patients, further supporting the presence of an ET-1-driven autocrine loop driving MC activation from IC.[67]

Repeat injection of engineered human Gd-IgA1 containing IC into immunodeficient mice caused mesangial hypercellularity associated with transcriptional activation of proinflammatory gene networks.[68] The dual ET_AR antagonist (ERA)/AngII type 1 receptor blocker sparsentan attenuated these responses, supporting the potential effect of ET_AR inhibition to attenuate MC activation in response to IgA IC.[68]

Anti-Thy1.1 antibody administration is a model of mesangioproliferative glomerulonephritis where IC-mediated MC injury causes inflammation, MC hyperproliferation, accumulation of mesangial matrix, and proteinuria, all key features of the MC response in IgAN.[69] Glomeruli from anti-Thy1.1 induced rats had increased ET-1 protein and mRNA expression that correlated with the level of glomerular proliferation,[70] whereas ET_AR blockade attenuated MC hyperproliferation.[71]

The immediate source of glomerular ET-1 overproduction was infiltrating macrophages; however, MCs were the dominant source of ET-1 throughout the hyperproliferative phase, suggesting that ET-1 functions as a potent mitogen for MCs *in vivo* following targeted MC injury by IC.

Atrasentan significantly reduced proteinuria and glomerular injury in the rat anti-Thy1.1 model.[72] Atrasentan also reversed pathogenic intrarenal transcriptional network induction of proinflammatory and profibrotic genes and decreases in genes involved in metabolism (oxidative phosphorylation and fatty acid metabolism); this pattern of gene expression is consistent with the dysregulated glomerular transcriptome of kidney biopsy samples from patients with IgAN (GSE104066). Furthermore, atrasentan reduced the tubulointerstitial injury score and the impairment in proximal tubular epithelial cell repair gene expression.[73]

Long-term treatment with an ET_AR antagonist ameliorated proteinuria, glomerular hypercellularity, and mesangial expansion in the ddY mouse model of IgAN.[66] Subsequently, ddY mice were bred to obtain grouped ddY (gddY) mice with early onset and nearly 100% incidence of IgAN.[74] Treatment with the dual ERA/AngII type 1 receptor blocker sparsentan for 8 weeks significantly reduced albuminuria and glomerulosclerosis in gddY mice.[75] Notably, this group found that sparsentan ameliorated the reduction in podocyte number and glycocalyx in gddY mice to a greater extent than losartan.[76] Treatment with atrasentan for 5 days reduced albuminuria in the gddY mouse and downregulated proliferative, inflammatory, and fibrotic gene networks, while restoring expression of pathways associated with metabolism[77]; the same transcriptional pathways were dysregulated in glomeruli from patients with IgAN (GSE141295 and GSE93798). Single cell RNA sequencing of the kidney from gddY mice following chronic treatment with atrasentan provided additional mechanistic insights.[72] Interestingly, failed repair proximal tubular epithelial cells were identified as the most expanded kidney specific cell type in gddY mice and had the most differentially expressed genes compared to control. Ligand-receptor interaction analysis suggests that these failed repair proximal tubular epithelial cells are a key source of cytokines and chemokines, leading to immune cell recruitment and fibroblast activation. Atrasentan reversed the pathogenic gene expression changes in failed repair proximal tubular epithelial cells that were induced in the IgAN model; in contrast, enalapril had minimal impact.[78] Lastly, an atrasentan transcriptional response signature was generated from failed repair proximal tubular epithelial cells to quantify atrasentan sensitive gene pathways in the molecular profiles generated from kidney biopsies in patients with IgAN from the NURTuRE CKD cohort[65]; the atrasentan signature score from IgAN patient kidney biopsies significantly correlated with eGFR, proteinuria, tubular atrophy, and interstitial fibrosis.

Clinical Trials Involving ET_AR Antagonists in IgAN

Several phase 2 and 3 clinical trials are evaluating the safety and efficacy of ERAs in IgAN (Table 1). The PROTECT trial evaluated the dual acting AngII type 1 receptor blocker-ERA sparsentan (trial details in Table 1) and demonstrated that sparsentan reduced proteinuria by 49.8%, compared with 15.1% by irbesartan, at 36 weeks in 404 patients.[59] This prespecified interim analysis led to the accelerated approval of sparsentan from the US Food and Drug Administration (FDA) in February 2023 for the treatment of IgAN.[79] The specific wording of the FDA approval states that sparsentan was approved in IgAN patients "at risk for rapid disease progression, generally a urine protein-to-creatinine ratio $\geq$1.5 g/g." Such accelerated approval for proteinuria reduction is based on its emergence as a reliable and, perhaps more importantly, modifiable risk factor for kidney disease progression[80]; data from large global cohorts support a strong relationship between sustained proteinuria reduction and preservation of kidney function. These data led the FDA and European Medicines Agency to accept proteinuria reduction as a reasonably likely surrogate for the treatment effect of therapies on long term kidney function outcome in IgAN, and a basis for accelerated approval (FDA) and conditional market approval (European Medicines Agency).[81] Final FDA approval for sparsentan in IgAN is pending confirmatory endpoint results on the rate of change of eGFR at 110 weeks post-randomization. In the PROTECT trial, sparsentan was generally well tolerated and there was no increase in body weight, as a proxy for fluid retention, compared to irbesartan; however, there was a small imbalance in the proportion of patients with mild edema as reported by investigators (14% sparsentan vs. 9% irbesartan).

In the AFFINITY trial, an open-label basket study in proteinuric glomerular diseases, atrasentan was associated with 54.7% reduction in proteinuria at 24 weeks ($N = 19$) in the IgAN cohort taking maximally tolerated doses (MTD) of RAS inhibitors (Table 1).[60] The ALIGN phase 3 trial is ongoing and will assess the effect of 0.75 mg/day of atrasentan versus placebo in patients with IgAN taking maximally tolerated doses of RAS inhibitors on proteinuria at 36 weeks and change in eGFR at 136 weeks (Table 1).[82] How ERAs are ultimately incorporated into treatment guidelines for IgAN will

Table 1. Clinical trials with endothelin A receptor antagonists in IgA nephropathy and chronic kidney disease

Clinical Trial	ClinicalTrials.gov Identifier	Clinical Phase	Sponsor	Population	Intervention/Comparator	Outcome	Additional Comments
PROTECT	NCT03762850	Phase 3	Travere Therapeutics	• Biopsy proven IgAN • $N = 404$ • >18 yrs • Proteinuria ≥1 g/d • eGFR ≥30 ml/min per 1.73 m^2	110 weeks of sparsentan vs. irbesartan	Change in UPCR from baseline to Week 36 Rate of change in eGFR from 6 weeks to 110 weeks post-randomization	
EPPIK[a]	NCT05003986	Phase 2	Travere therapeutics	• Biopsy proven IgAN • $N =$ up to 27 • ≥1 yrs to <18 yrs • Proteinuria: • UPCR ≥0.6 g/g • eGFR ≥30 ml/min per 1.73 m^2	108 weeks of sparsentan	Incidence of TEAEs, SAEs, & AEs leading to treatment discontinuation, and AEOIs Change in UPCR over 108 weeks	
SPARTAN	NCT04663204	Phase 2	Travere therapeutics	• Biopsy proven IgAN • $N = 10$ • >18 yrs • Proteinuria ≥0.5 g/d • eGFR ≥30 ml/min per 1.73 m^2	110 weeks of sparsentan	Change in UPCR from baseline to week 36 Rate of change of eGFR over 52- and 104 weeks	No RASi within 12 mos
ALIGN	NCT04573478	Phase 3	Chinook therapeutics	• Biopsy proven IgAN • $N = 320$ planned • >18 yrs • Proteinuria ≥1 g/d • eGFR ≥30 ml/min per 1.73 m^2	136 weeks of atrasentan vs. placebo	Change in UPCR from baseline to week 36 Change from baseline to end of study in eGFR	MTD of RASi
AFFINITY[b]	NCT04573920	Phase 2	Chinook therapeutics	• Biopsy proven IgAN • $N = 20$ • >18 yrs • UPCR 0.5 to <1.0 g/g • eGFR ≥30 ml/min per 1.73 m^2	52 weeks of atrasentan	Change in UPCR from baseline to week 12	MTD of RASi
ASSIST	NCT05834738	Phase 2	Chinook therapeutics	• Biopsy proven IgAN • $N = 52$ • >18 yrs • Proteinuria ≥0.5 g/d on SGLT2i • eGFR ≥30 ml/min per 1.73 m^2	24 weeks of atrasentan vs. placebo (crossover at 12 weeks)	Change in UPCR to week 12	MTD of RASi All patients on SGLT2i
ZENITH-CKD[c]	NCT04724837	Phase 2	AstraZeneca	• Chronic kidney disease • $N = 495$ • >18 yrs • UACR ≥150 & ≤5000 mg/g • eGFR ≥20 ml/min per 1.73 m^2	12 weeks of zibotentan & dapagliflozin	Change in UACR from baseline to week 12	On RASi or MRA

AE, adverse events; AEOI, adverse events of interest; eGFR, estimated glomerular filtration rate; mos, months; MRA, mineralocorticoid antagonist; MTD, maximum tolerated doses; RASi, renin-angiotensin system inhibitor; SAE, serious adverse events; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TEAE, treatment emergent adverse events; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio; yrs, years.

[a]The EPPIK Study is enrolling 57 children and young adults with focal segmental glomerulosclerosis (FSGS), minimal change disease (Population 1, $n = 30$), and IgA nephropathy (IgAN), IgA vasculitis and Alport syndrome (Population 2, $n = 27$); recruitment in each population is based on order of enrollment, not disease type.

[b]The Affinity Study is enrolling 100 adults with FSGS ($n = 40$), IgAN ($n = 20$), diabetic kidney disease ($n = 20$) on SGLT2i, and Alport syndrome ($n = 20$).

[c]The Zenith-CKD study is enrolling 495 adults with chronic kidney disease of any cause, of which some will have IgAN.

depend not only on their renoprotective effects but also on how well they combine with other therapies to reduce the lifetime risk of kidney failure in IgAN.

Adverse Events Associated With ET_AR Receptor Blockade

Endothelin receptor antagonists have been associated with adverse events. The incidence and severity of these events may depend on the chemical structure, dose, patient characteristics, and use of other drugs.

As a class, ERAs have the potential for teratogenicity, thus their use carries a requirement for birth control in patients of childbearing potential. To our knowledge, there are no peer-reviewed publications on ERAs and male fertility. Bosentan, a combined ET_AR/ET_BR antagonist, was reported to reduce sperm count in a minority of patients that normalized with drug discontinuation.[83]

Some ET receptor antagonists, whether an ERA or combined ET_AR/ET_BR antagonist, have been associated with elevated markers of liver injury.[84] The mechanisms are uncertain but may involve effects on hepatobiliary transporters and metabolism.[85] In a post-hoc analysis of the Study of Diabetic Nephropathy with Atrasentan trial involving over 3600 patients with type 2 diabetes and CKD, atrasentan was not associated with liver-related treatment emergent adverse events and, in fact, modestly reduced serum aspartate transferase, alanine transaminase and alkaline phosphatase levels.[86] Sparsentan use has also not been associated with hepatotoxicity; however, with the accelerated approval of sparsentan, the FDA mandated a Risk Evaluation and Mitigation Strategy for potential hepatotoxicity, stating that some ET receptor antagonists have caused hepatotoxicity.[79]

Many ET receptor antagonists, whether an ERA or combined ET_AR/ET_BR antagonist, cause fluid retention that typically occurs within a few weeks of initiating treatment and manifests as hemodilutional anemia, weight gain, and/or edema. The fluid retention is dose-dependent; however, maximal antiproteinuric effects can be obtained at ERA doses much lower than those causing maximal fluid retention.[87] Importantly, fluid retention severity is associated with comorbid cardiovascular conditions. The Study of Diabetic Nephropathy with Atrasentan trial found numerically increased, albeit not statistically significant, hospitalization for heart failure associated with atrasentan treatment in a high risk diabetic kidney disease population.[88] Related to this, baseline and early changes in brain natriuretic peptide levels in response to atrasentan predicted heart failure hospitalization in the Study of Diabetic Nephropathy with Atrasentan,[89] indicating that brain natriuretic peptide monitoring with ERA initiation may be important in patients at higher risk of heart failure. In contrast, no heart failure and insignificant weight gain have been observed thus far in patients with IgAN in the PROTECT and AFFINITY trials (a population with much fewer cardiovascular comorbidities).[59] Therefore, careful patient selection and ERA dosing, timely administration of diuretics, and appropriate monitoring are indicated.

ET_AR Blockade in the Current and Emerging Treatment of IgAN

The Kidney Diseases: Improving Global Outcomes 2021 guideline for glomerular diseases recommends supportive care, including lifestyle measures and RAS blockade for every patient with IgAN, and enrollment in a clinical trial for those who remain at high risk of progressive kidney failure.[90] These guidelines are being updated in 2023 and will consider new clinical trial data published over the past 3 years.

SGLT2i reduce the risk of major kidney outcomes in patients with CKD with and without type 2 diabetes[91-93] and are recommended by clinical practice guidelines for the treatment of CKD, irrespective of diabetes status. Although there are no dedicated trials to assess the efficacy and safety of SGLT2i in patients with IgAN, *post hoc* and pooled analyses from the 2 large kidney outcome trials, DAPA-CKD and EMPA-Kidney, reported that the beneficial effects of SGLT2i in slowing the progression of CKD was consistent, irrespective of the underlying kidney disease etiology, including IgAN.[93,94] Specifically, combining the data from >1000 patients with IgAN participating in the 2 clinical trials, SGLT2 inhibition with dapagliflozin or empagliflozin reduced the risk of 50% GFR decline, kidney failure or death due to cardiovascular disease or kidney failure by 40%.[95] These strong and consistent benefits may explain the uptake of SGLT2i in clinical practice as observed in clinical registry reports.

Because of the diuretic effects of SGLT2i, combining an ERA with SGLT2i holds promise to augment nephroprotection, due to activation of different pathways, and potentially mitigating fluid retention. Indeed, in a small subset of patients from the Study of Diabetic Nephropathy with Atrasentan trial, combined initiation of atrasentan and SGLT2i inhibition was associated with a larger reduction in albuminuria and reduction in body weight compared to atrasentan alone in patients with type 2 diabetes and CKD.[96] Combination use of SGLT2i with ERAs in IgAN is being evaluated in the ASSIST trial and the open label extension of the PROTECT trial (Table 1). Patients with IgAN are also being recruited to the ZENITH-CKD trial (Table 1). In addition, in the ongoing phase 3 ALIGN trial (Table 1) to assess efficacy and safety of atrasentan, a separate

stratum of patients with IgAN using SGLT2i is being enrolled to document long-term effects of atrasentan compared to placebo on top of SGLT2 inhibition.

With the publication of the TESTING trial, there has been a renewed discussion on the safety and efficacy of systemic corticosteroids in IgAN.[97,98] Treatment emergent toxicity and poor tolerability of systemic corticosteroids limit their utility in IgAN and prevent repeated treatment over the lifetime of the patient. An emerging option is the use of complement blockade to reduce glomerular inflammation driven by activation of the lectin and/or alternative complement pathways in IgAN.[99] A different therapeutic approach currently being explored in IgAN is the targeting of pathogenic IgA producing B/plasma cells, either using a specific formulation of gut-directed budesonide, Nefecon, or by inhibiting signaling through B cell-activating factor of the TNF family and/or APRIL pathways. Data from the phase 3 NefIgArd trial reported that after 9 months, proteinuria was 27% lower in the Nefecon group compared with placebo and this was associated with a reduction in the pathogenic form of IgA.[100] Similarly, data from early phase studies of sibeprenlimab, zigakibart, atacicept, and telitacicept support an antiproteinuric effect of B cell-activating factor of the TNF family and/or APRIL blockade alongside significant reductions in pathogenic IgA levels.[101-104]

These are promising new therapeutic approaches; however, most of the ongoing trials will not be finished until 2025, at the earliest. If these trials show beneficial effects of different, and possibly complementary, therapeutic approaches that target different stages of the pathophysiological cascade in IgAN, a major clinical question for the future will be how to define the best combination. Based on the clinical trial data thus far for IgAN, it is unlikely that any single agent, or a combination of agents that solely target the cause (IC) or renal consequences of IgAN, will be sufficient to maintain an eGFR loss <1 ml/min per 1.73 m^2. Furthermore, it will be essential to define the optimal therapeutic approach for each patient in accord with the concept of personalized medicine. Several initiatives have started that aim to individualize treatment based on patient characteristics and deep phenotyping. The NEPTUNE-Match platform clinical trial (NCT04571658), for example, randomizes patients with IgAN to interventions they are predicted to most likely benefit from based on their clinical characteristics and biopsy data. Lessons from this and other trials are vital to improve and personalize future therapy for IgAN and define the role of ERAs in the future IgAN treatment landscape.

DISCLOSURE

DEK and JB are consultants for AstraZeneca, Chinook Therapeutics and Travere Therapeutics. HJLH Is a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Chinook Therapeutics, CSL Behring, Dimerix, Eli Lilly, Gilead, Janssen, Merck, Novartis, NovoNordisk, and Travere Therapeutics; and has received research support from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, and NovoNordisk to conduct clinical trials. KNC is a consultant for AstraZeneca, Calliditas, Chinook Therapeutics, Sanofi, and Travere Therapeutics. DR is a consultant for Novartis, George Clinical, Otsuka Pharmaceuticals (Visterra), Calliditas Therapeutics (Pharmalinks), Angion Biomedica, Catalyst Biosciences, Eledon Pharmaceuticals, and Chinook Therapeutics; has received research funding from Reata Pharmaceuticals, Travere Therapeutics, Achillion Pharmaceuticals, Pfizer Pharmaceuticals, Calliditas Therapeutics (Pharmalinks), Otsuka Pharmaceuticals (Visterra), Vertex Pharmaceuticals, and Chinook Therapeutics; and has ownership in Reliant Glycosciences, LLC. MC, IO, RHM and AK are employees of Chinook Therapeutics.

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