IgA Nephropathy Disease
Pathophysiology: Focus on Endothelin-1 and Angiotensin II
Multiple Factors Are Involved in the Pathogenesis of IgA Nephropathy: Multi-Hit Model

Many factors may influence susceptibility to the development and pathogenesis of IgA nephropathy, including genetic factors, environmental factors, and lifestyle factors.

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA₁ = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

Multiple Factors Are Involved in the Pathogenesis of IgA Nephropathy: Multi-Hit Model

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Patients with IgA nephropathy have underglycosylated IgA1, resulting in increased levels of circulating galactose-deficient IgA1.1–4
Multiple Factors Are Involved in the Pathogenesis of IgA Nephropathy: Multi-Hit Model

IgG and/or IgA isotype antibodies are synthesized; these antibodies recognize and bind to galactose-deficient IgA₁, forming immune complexes¹–⁴

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ET-1 and Ang II Play a Key Role in the Pathophysiology of IgA Nephropathy

Immune complexes are deposited in the mesangium to cause glomerular injury by:1,2

- Mesangial cell proliferation
- Pro-inflammatory and pro-fibrotic cytokine secretion
- Extracellular matrix production
- Upregulation of growth factors, including ET-1 and Ang II

Through cross-talk, Ang II upregulates ET-1 production and ET-1 increases the conversion of Ang I to Ang II3

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

ET-1 and Ang II Play a Key Role in the Pathophysiology of IgA Nephropathy

ET-1 and Ang II act in tandem via their receptors, ETAR and AT₁R, to amplify glomerular injury via:¹,²

- Mesangial cell proliferation
- Inflammation
- Extracellular matrix production
- Podocyte injury and apoptosis
- Detrimental changes in glomerular hemodynamics

Ang II = angiotensin II; AT₁R = angiotensin II subtype 1 receptor; ET-1 = endothelin-1; ETAR = endothelin-1 type A receptor; IgA = immunoglobulin A; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.


ET-1 and Ang II Play a Key Role in the Pathophysiology of IgA Nephropathy

As a result of glomerular injury, the glomerular filtration barrier is compromised, leading to proteinuria, hematuria, and glomerulosclerosis.

Proteinuria further increases ET-1 and Ang II levels.

Elevated proteinuria over time is associated with reduction in eGFR and greater risk of progression in IgA nephropathy.

Ang II = angiotensin II; eGFR = estimated glomerular filtration rate; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

Proteinuria Drives Further Injury in the Tubulointerstitial Compartment

After entering the urinary space, leaked proteins and IgA$_1$-containing immune complexes drive tubular atrophy and interstitial fibrosis$^1$

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA$_1$ = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

Sparsentan* is a dual endothelin angiotensin receptor antagonist, or DEARA.

* Sparsentan has received accelerated approval from the US FDA for the reduction of proteinuria in adults with primary IgA nephropathy at risk of rapid disease progression.

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA1 = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

Sparsentan is a non-immunosuppressive, highly selective dual antagonist of both endothelin-1 type A receptors (ET\textsubscript{A}R) and angiotensin II subtype 1 receptors (AT\textsubscript{1}R)\textsuperscript{1-3}

* Sparsentan has received accelerated approval from the US FDA for the reduction of proteinuria in adults with primary IgA nephropathy at risk of rapid disease progression.

Ang II = angiotensin II; AT\textsubscript{1}R = angiotensin II subtype 1 receptor; ET-1 = endothelin-1; ET\textsubscript{A}R = endothelin-1 type A receptor.


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Effects of ET₁R and AT₁R in the Pathophysiology of Glomerular Disease*

Sparsentan Significantly Attenuated Albuminuria and Glomerulosclerosis in Experimental IgA Nephropathy

The effect of sparsentan on albuminuria and glomerulosclerosis in gddY mice over 16 weeks of treatment

**Sparsentan Significantly Attenuated Albuminuria Compared with Control-(p<0.0001) and Losartan-Treated Mice (p<0.001) (Over 10 Weeks of Treatment*)**

**Sparsentan Significantly Reduced Glomerulosclerosis Compared with Control-(p<0.0001) and Losartan-Treated Mice (p<0.001)**

**ACR = albumin-to-creatinine ratio; C = control; IgA = immunoglobulin A; IgG = immunoglobulin G; LS30 = losartan 30 mg/kg drinking water; SP900 = sparsentan 900 ppm in diet; UACR = urinary albumin-to-creatinine ratio.**

gddY mice are prone to developing IgA nephropathy. The mice studied in the gddY mouse model develop albuminuria between 4 and 8 weeks of age; glomerular IgA, IgG, and C3 deposits; and glomerular injury.

Sparsentan Demonstrated Renoprotective Effects in IgA Nephropathy

The effect of sparsentan on albuminuria and glomerulosclerosis in gddY mice over 16 weeks of treatment

Effect of sparsentan on podocytes and glycocalyx

Podocyte number (WT-1 staining)

Glycocalyx area (FITC-labeled lectin)

Podocyte number was significantly increased in sparsentan-treated mice (p<0.0001 vs control and losartan) and similar to healthy BALB/c mice

Loss of the glycocalyx area was significantly decreased in sparsentan-treated mice (p<0.0001 vs control and losartan)

**** p<0.0001; #### p<0.0001 vs BALB/c; $ p<0.05; $$$ p<0.001; $$$$ p<0.0001 vs LS30.
BALB/c = healthy control mice; C = control; FITC = fluorescein isothiocyanate; IgA = immunoglobulin A; LS30 = losartan 30 mg/kg drinking water; SP900 = sparsentan 900 ppm in diet; WT-1 = Wilms tumor gene 1.
Sparsentan Attenuated Glomerular Cellularity in Experimental IgA Nephropathy

The protective effects of sparsentan on a glomerular injury-induced mouse model of IgA nephropathy*

* Gd-IgA1 and rIgG (200 mg Gd-IgA1 and 100 mg rIgG) were used to form EIC in murine serum and were intravenously injected into ~7-week-old mice every other day for a total of 6 doses. Sparsentan was given by oral gavage once daily at 60 or 120 mg/kg (SP60 or SP120) with dosing commencing on the first day of the EIC injections.

EIC = engineered immune complexes; EIC-V = mice receiving EIC injection and vehicle; Gd-IgA1 = galactose-deficient immunoglobulin A subclass 1; IgA = immunoglobulin A; rIgG = recombinant immunoglobulin G; SP = sparsentan; V = vehicle. Jenkinson C, et al. WCN 2019; poster presentation (abstract SAT-010).

EIC-mediated increase in cellularity (shown by number of nuclei/glomerulus) was significantly attenuated in mice treated with sparsentan at doses 60 and 120 mg/kg (p<0.05 vs EIC-V)

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Sparsentan Downregulated the Expression of Inflammatory Genes in a Mouse Model of IgA Nephropathy

**The effects of sparsentan on gene transcription in an experimental mouse model of IgA nephropathy**

Pathway-level analysis of inflammatory processes

<table>
<thead>
<tr>
<th>Up Pathways</th>
<th>Down Pathways</th>
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<tbody>
<tr>
<td>Control vs. EIC</td>
<td>EIC vs. EIC+S120</td>
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<tr>
<td><strong>Pathway</strong></td>
<td><strong>p value</strong></td>
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<td>Cytokine signaling</td>
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<tr>
<td>Cellular response to INF1</td>
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<td>MHCI-mediated Ag response</td>
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<td>Response to IFNγ</td>
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<tr>
<td>Cytokine response</td>
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</tbody>
</table>

* EIC were injected into ~7-week-old mice every other day for a total of 6 doses (n=5/group) via tail vein; † WGCNA analysis between grouped pairs (control vs EIC, control vs EIC+S120, control vs EIC+S60) was performed to find module eigengenes that correlate with nuclei per glomerulus and Ki67 positivity. Genes from modules significantly associated with cellular phenotypes (p-adj.<0.05) were then cross-compared with DESeq2 LFC analysis.

Vehicle or sparsentan (60 [S60] or 120 [S120] mg/kg) was given by gavage once daily from the first day of EIC injections. Negative-control mice only received vehicle. Ag = antigen; EIC = engineered immune complexes; IFN = interferon; IgA = immunoglobulin A; MHC = major histocompatibility; TAP = transporter associated with antigen processing. Reily C, et al. ASN 2021; poster presentation (abstract PO1454).
ET-1 and Ang II play a key role in the pathophysiology of IgA nephropathy; ET-1, acting via ET$_A$R, and Ang II, acting via AT$_1$R, are involved in multiple pathophysiologic processes that lead to kidney dysfunction and CKD.

ET-1 and Ang II act in tandem to amplify the inflammatory cytokine response and potentiate glomerular dysfunction, tubulointerstitial injury, and vascular dysfunction, worsening proteinuria and resulting in a progressive decline in kidney function.

Sparsentan is a novel dual endothelin angiotensin receptor antagonist (DEARA), which attenuated albuminuria and glomerulosclerosis in preclinical studies of IgA nephropathy.

Sparsentan has received accelerated approval from the US FDA for the reduction of proteinuria in adults with primary IgA nephropathy at risk of rapid disease progression (UP/C ≥ 1.5 g/g).