Therapeutic Approaches to Chronic Kidney Disease—Beyond the RAS

• Despite improvements in glycemia and BP control, and the efficacy of RAS blockade, a substantial number of patients will progress to ESRD.
• This finding is consistent that key pathogenetic mechanisms leading to progression of renal disease are not modified or inactivated by current therapeutic approaches.
• Understanding the key mechanisms leading to progressive CKD and developing nephroprotective agents is critical to slowing the progression of this deadly process.
ON-TARGET Trial: Dual RAS Therapy with Ramipril and Telmisartan Failed to Decrease Vascular Events

Baseline UACR 929 mg/g CR

ALTITUDE Trial: Dual RAAS Therapy with Aliskiren and ACEi/ARB Failed to Decrease Vascular Events

Baseline UACR 206 mg/g CR
VA-NEPHRON-D Trial: Dual RAAS Therapy with Losartan and Lisinopril Did Not Provide an Overall Clinical Benefit

Baseline UACR 862 mg/g CR
Therapeutics Identified in the Inflammatory Pathway

Hyperglycemia

Inflammatory state

Increased NF-κB expression

- NF-κB inhibitors
  - Thiazolidinediones (rosiglitazone, pioglitazone)
  - 1,25-Dihydroxyvitamin D3

Increased JAK/STAT pathway transcription

- JAK1/JAK2 inhibitor (baricitinib)

Increased expression of inflammatory cytokines

- IL-1, IL-6, IL-18
  - MMF, turmeric

- TNF-α
  - TNF-α inhibitors
    - etanercept, infliximab, pentoxifylline, silymarin
Therapeutic Agents Identified in the Metabolic and Alternative Pathways
Indoxyl Sulfate

- Indoxyl sulfate is derived from dietary proteins
- Uremic toxin which stimulates glomerular sclerosis and interstitial fibrosis
- Increases reactive oxygen species production in tubular cells and increases NAD(P)H oxidase activity in endothelial cells
- Orally administered spherical carbon adsorbent AST-120 reduces “uremic toxins”, like indoxyl sulfate, and is used in patients with CRF
Metabolism of Indoxyl Sulfate and Effect of AST-120

Liver

Indoxyl sulfate (oxidation and sulfation)

Dietary protein → Tryptophan → Indole

Large intestine

E. coli

AST-120 (Kremezin)

Feces

Blood

Kidney

Urine

CKD

EPPIC Trials of AST-120: NO Additional Benefit to Standard of Care in CKD

SUN Trial: Sulodexide (Heparan and Chondroitin Sulfates) Failed to Demonstrate Renoprotection in Overt Type 2 Diabetic Nephropathy

Baseline UACR ~1000 mg/g CR
BEACON Study: Bardoxolone Methyl Increased CV Deaths in Type 2 Diabetes and Stage 4 CKD

TREAT Trial: Darbepoetin Alfa Failed to Demonstrate Renoprotection in Overt Type 2 Diabetic Nephropathy

Death from Any Cause

Hazard ratio, 1.05 (95% CI, 0.92–1.21)  
\[ P=0.48 \]

No. at Risk

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