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Urinary Oxalate in Primary Hyperoxaluria

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Primary Hyperoxalururia (PH)  
Genetic and Pathophysiologic Basis

**Autosomal recessive inheritance**
- Prevalence 1-3:10^6
- Incidence rate 1:10^5 births/yr

**Endogenous oxalate synthesis in hepatocytes**
- PH type 1: Peroxisomal AGT deficiency
- PH type 2: Cytosolic GRHPR deficiency

Pathology due to excessive production of endogenous oxalate, and excretion of this metabolic end product through the kidneys.
Disease Process a Consequence of Hyperoxaluria

- Damage to renal parenchymal cells
  - Oxalate toxicity
  - CaOx crystals
- Frequent nephrolithiasis
- Nephrocalcinosis
- Decline in renal function
- ESRD
- Systemic oxalosis
- Premature death
Current Therapeutic Strategies Aim at Lowering Urinary Oxalate

**Reduce Urinary Oxalate and its Damage to the Kidneys**

- **Enzyme deficiency**
  - Liver transplant
  - Pyridoxin

- **Liver synthesis**
  - Oxalate degradation

- **Colon**
  - Oxalate degradation

- **Kidney**
  - Oxalate excretion
  - Hyperhydration
  - CaOx inhibitors
  - Stone removal
  - Dialysis
  - Transplant
  - Kidney failure

**Enteric elimination of oxalate**

- Colonic degradation of oxalate may provide a suitable trans-epithelial gradient for the enteric elimination of endogenous oxalate
- Mechanism confirmed in animal models
  - AGTX knock-out mice
  - Nephrectomized hyperoxaluric rats
Disease Progression Related to Urinary Oxalate

Renal survival influenced by the degree of hyperoxaluria

- Disease progression reversed by liver transplantation
  - Improved kidney graft survival with combined liver/kidney transplant vs. isolated kidney transplant. (Bergstrahl 2010)
  - Renal deterioration is halted or even reversed by pre-emptive isolated liver transplantation in patients with residual renal function. (Brinkert 2009, Nolkemper 2000)

68 patients enrolled in IRPH had UOx measured at diagnosis, while renal function was maintained. Those with UOx of less than 1.2 mM/day had a 92% 20y renal survival after diagnosis, vs. 72% for those with UOx above this level. (Milliner 2006)
Valid and reliable assays are well established and widely used in clinical practice

- Variability from sampling has been a bigger concern
  - 24h urine collections
  - Preservation of urine

**Sampling compartment (urine) predicts disease compartment (kidney)**

- Urinary oxalate is an end-product of metabolism that damages the kidneys
Supportive Data on Surrogate Endpoint

Endpoint confirmed in animal models
- AGTX knock-out mice
- Nephrectomized hyperoxaluric rats

Endpoint supported in patients
- PH type 1
- ESRD patients
- Infantile oxalosis

Clinical Features Associated with Hyperoxalurias - Crosssectional Data

<table>
<thead>
<tr>
<th>Category</th>
<th>UOx (mM/day)</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH type 1</td>
<td>1.0 - 4.0</td>
<td>ESRD/Systemic Oxalosis</td>
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<tr>
<td></td>
<td></td>
<td>Nephrocalcinosis</td>
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<tr>
<td></td>
<td></td>
<td>Frequent nephrolithiasis</td>
</tr>
<tr>
<td>PH type 2</td>
<td>1.0 - 2.0</td>
<td>Renal damage</td>
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<td></td>
<td></td>
<td>Frequent nephrolithiasis</td>
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<tr>
<td>Post-bariatric surgery</td>
<td>0.8 - 1.2</td>
<td>Possible renal damage</td>
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<td>Recurrent nephrolithiasis</td>
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<tr>
<td>Idiopathic Hyperoxaluria</td>
<td>0.4 - 0.5</td>
<td>Preserved renal function</td>
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<tr>
<td></td>
<td></td>
<td>Sporadic nephrolithiasis</td>
</tr>
<tr>
<td>Normal</td>
<td>0.1 - 0.4</td>
<td></td>
</tr>
</tbody>
</table>
Surrogate endpoint qualification

- Disease criteria
- Drug criteria
- Biomarker criteria
- Data criteria

Urinary oxalate was accepted as a surrogate endpoint

- Compelling reduction in UOx needed
- Trends in secondary endpoints reflecting clinical benefit needed
- Accelerated approval to be evaluated
References