The Primary Hyperoxalurias
2019 Update
The Past, the Present, and A Glimpse to the Future

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The Primary Hyperoxalurias (PH)

A family of rare, inherited, liver-derived metabolic disorders resulting in oxalate overproduction

PH Type 1:  Most common, most serious
            Median age of kidney failure mid-20s
            Systemic oxalosis

PH Type 2:  Less common, serious
            Chronic stones, some patients with kidney failure

PH Type 3:  Chronic stones, especially in youth

**Disease Progression of PH Type 1 (PH1)**

- Abnormal liver metabolism produces *excess oxalate*
- Calcium *oxalate crystals form in the kidneys*
- Decline in kidney function results in *systemic oxalosis*
- Median age of onset of *kidney failure* is 23 yrs
- Patients *require intensive daily dialysis* while awaiting a *liver-kidney transplant*

**Systemic Oxalosis in PH1**

Primary Hyperoxaluria Type 1 (PH1)

- Autosomal recessive disorder of AGXT gene that encodes AGT protein

Oxalate
(Crystalizes in kidneys in PH1 & causes damage)

Liver cell metabolism

Defective glyoxylate-reductase

- GRHPR, 9p11
- Not liver specific
- Increased urinary oxalate and glycerate
- Recurrent urolithiasis

“Benign” follow up

- 20% of patients with ESRD
Defective Hydroxy-2-oxoglutarate aldolase 1

- HOGA1, 10q24.1
- Increased urinary oxalate and HOG
- Severe Urolithiasis
- Remission of symptoms despite hyperoxaluria
- Very low incidence of ESRD
Primary Hyperoxaluria Type 1
Epidemiology

PH1 is an ultra rare disease
- Estimated prevalence & genotypic incidence:
  - 1-3 cases per million pop (diagnosed today in EU countries)
  - 1 case per ~150,000 births (based on disease allele frequency)

Over 1,000 PH1 patients in two registries

330 PH1 pts
July 2015

683 PH1 pts
July 2015

P. Cochat et al. 2013. NEJM 369;7;

Median age of diagnosis is 12 years

http://www.rarekidneystones.org/hyperoxaluria/physicians.html;
Tang 2014, Kidney International

Urinary oxalate excretion rate of >2 mmol/1.73m²/24hr associated with a significantly higher rate of end stage renal disease (ESRD)

eGFR at Diagnosis is Already Compromised in PH-1

Possible Mechanisms of AKI/CKD related to PH

- Urinary supersaturation
  - Collecting system obstruction by kidney stone
  - Vasoconstriction
    - Renal hypoperfusion
  - Intratubular obstruction
  - Intratubular crystallization
    - Direct cell injury
      - Indirect cell injury
        - Oxidative stress pathway
        - Inflammasome pathway

- Acute and chronic kidney injury
Urinary Inflammasome is Upregulated by Oxalate

Table 1. Trends and Differences in Proteomic Markers in PH1

<table>
<thead>
<tr>
<th>Variables</th>
<th>UOx&gt;Md</th>
<th>UOx&lt;Md</th>
<th>eGFR&gt;Md</th>
<th>eGFR&lt;Md</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1; IL-15</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>KIM-1, NGAL</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Apo C-III; B2 Microglobulin; CD40, CD40L; IL-1α; IGFBP-2; SOD-1; TNFR-2; VCAM-1; VEGF</td>
<td>↑</td>
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<td>↑</td>
<td>↑</td>
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<tr>
<td>Calgranulin, HGF, ICAM-1, IFN-γ, LOX-1, MMP-7, RANTES, TRAIL-3</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>OPN</td>
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<td>THP</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>α1AT, α1M, Fetuin A, IL-1β, IL-8, Microalbumin, TIMP-1</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>TFF-3</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>↑</td>
</tr>
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</table>
Medical Therapies Are Mostly Ineffective

- Reduce Urinary Ca-Ox supersaturation
  - High Fluid Volume
  - Citrate Therapy
  - Limit Hypercalciuria

- Use an Oxalate Specific Probiotic Bacteria (O. Formigenes)
  - Two Clinical Trials have not yielded positive results in patients with CKD.

A randomised Phase II/III study to evaluate the efficacy and safety of orally administered Oxalobacter formigenes to treat primary hyperoxaluria
Vitamin B6 in Homozygous Gly170Arg Patients with PH-1

Figure 1.

Absolute Uox Excretion in mmol/1.73 m²/d

Study Week 0 24 0 24 0 24

c.508G>A homozygous heterozygous negative

p = 0.05 p = 0.07 p = 0.42

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Current Best Rx: Enzyme Replacement Therapy with a Total Hepatectomy followed by a Liver Transplant
Urinary Oxalate remains elevated long after liver tx

*E.J. Bergstrahlh et al (2010)

**Figure 6:** Urinary oxalate readings (and running average, solid line) from 16 PH recipients of K+L transplants. Normal urine oxalate (<0.46 mmol/1.73m²BSA/24 hrs) is shown by the area shaded gray. Hyperoxaluria persisted in most patients for up to 3 years following transplantation. During the first year, marked hyperoxaluria was characteristic due to mobilization of preexisting tissue stores of calcium oxalate deposited during renal failure.
Plasma Oxalate remains elevated after transplantation

11 K+L recipients
6 K recipients

Figure 5: Plasma oxalate concentration declined rapidly following successful K+L (A) and K alone (B) transplantation, but remained above normal in most patients during the first year after transplant. The normal range for plasma oxalate levels (< 1.6 μmol/L) is shown in the area shaded gray.
What Lies Ahead?
HEPATIC OXALATE SYNTHESIS FROM HYP IN PH1

Hydroxyproline
\[ \xrightarrow{4 \times \text{Enz}} \]
Glyoxylate \[ \xrightarrow{\text{GR}} \]
Glycolate

Mito
Oxalate

Cyto
\[ \xrightarrow{\text{LDHA}} \]
Glycolate \[ \xrightarrow{\text{GR}} \]
Glyoxylate \[ \xrightarrow{\text{GO}} \]
Oxalate

H_2O_2

Glycine

Northwestern
HEPATIC OXALATE SYNTHESIS FROM HYP IN PH2

- Hydroxyproline → Glyoxylate
  - 4 x Enz → Oxalate
  - GXR → Oxalate

- Cyto: Glyoxylate → Oxalate
  - LDHA

- Perox: Glyoxylate → Glycine
  - AGT
Genes to Messenger RNA to Protein, Nucleus vs. Cytoplasm

mRNA is the target, not protein
RNA Interference (RNAi) to Reduce Target Gene Expression

- RNAi destroys a specific mRNA sequence copied from a specific gene
- The new siRNA delivered to hepatocytes gets incorporated in RISC and targets a specific mRNA
- Removing the target mRNA removes the target protein, yielding a therapeutic benefit

**RNAi is not gene therapy - the effect is temporary**
Human Lactate Dehydrogenase (LDH) Proteins and Nomenclature

- LDHA and LDHB are expressed at variable ratios throughout the body, LDHC is testes-specific

<table>
<thead>
<tr>
<th>Isoenzyme</th>
<th>LDH5</th>
<th>LDH4</th>
<th>LDH3</th>
<th>LDH2</th>
<th>LDH1</th>
<th>LDHC</th>
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<tr>
<td>old names</td>
<td>LDH-M₄</td>
<td>LDH-M₃H</td>
<td>LDH-M₃H₂</td>
<td>LDH-MH₃</td>
<td>LDH-H₄</td>
<td>LDH-X</td>
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<td>LDH tetramer</td>
<td>LDH-A₄</td>
<td>LDH-A₃B</td>
<td>LDH-A₃B₂</td>
<td>LDH-AB₂</td>
<td>LDH-B₄</td>
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<tr>
<td>Protein subunit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA</td>
<td>Hepatic target to treat PH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>Striated muscle, liver, other tissues</td>
<td></td>
<td>Heart, spleen, kidney, brain, other tissues</td>
<td></td>
<td></td>
<td>Testes only</td>
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</table>


* <1% in Schueren et al. eLife 2014;3:e03640
LDHA Silencing for the Treatment of the Primary Hyperoxalurias

A family of rare, inherited, liver enzyme deficiencies resulting in pathologic oxalate production

How LDHA silencing treats all forms of PH

- PH is excessive production of oxalate, which crystalizes and causes tissue damage
- Three enzymes, when deficient, lead to PH
  - AGT: deficiency causes PH1
  - GRHPR: deficiency causes PH2
  - HOGA: deficiency causes PH3
- These enzyme deficiencies lead excess glyoxylate
- Some excess glyoxylate is converted to oxalate by the LDHA enzyme
- LDHA silencing prevents oxalate production from glyoxylate, thus treating PH

DCR-PHXC silences the LDHA gene for the treatment of all forms of PH
PHYOX: Normalization or Near-Normalization of Uox in a Majority of Patients

• Cohort 1 (1.5 mg/kg):
  – 3/4 participants’ 24Hr Uox values reached near-normalization (<0.6 and ≥0.46 mmol/24Hr) at one or more post-dose time points
  – Mean maximal 24Hr Uox reduction = 50% (range: 39%-59%)
  – Per protocol, 2 participants are still in follow-up as of postdose Day 85, as their 24Hr Uox has not yet returned to within 80% of the lowest baseline 24Hr Uox measurement

• Cohort 2 (3.0 mg/kg):
  – 3/4 participants’ 24Hr Uox values have reached normalization (<0.46 mmol/24Hr) at one or more postdose time points
  – Mean maximal 24Hr Uox reduction = 65% (range: 56%-80%)
  – 3 participants are still in follow-up and may not yet have reached maximal 24Hr Uox reductions

• Cohort 3 (6.0 mg/kg):
  – As of October 1, 2018 data cut, only 1 participant has 24Hr Uox results
  – Maximum reduction for that 1 participant = 64% as of postdose Day 43
Using the Gut for Oxalate Transfer

Use of a Bacterial Product, OC5 from O Formigines

OxThera Intellectual Property AB, Sweden

Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Race/Ethnicity</th>
<th>BMI (kg/m²)</th>
<th>Time* since PH diagnosis (months)</th>
<th>Dialysis Mode</th>
<th>Time* on dialysis (months)</th>
<th>Dialysis frequency b</th>
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</thead>
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<tr>
<td>SCR02-0002</td>
<td>58</td>
<td>Male</td>
<td>Caucasian</td>
<td>19.9</td>
<td>3.2</td>
<td>HD only</td>
<td>3.5</td>
<td>3/week</td>
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<td>SCR02-0004</td>
<td>20</td>
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<td>Middle Eastern</td>
<td>21.8</td>
<td>33.3</td>
<td>HD only</td>
<td>56.8</td>
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<td>Male</td>
<td>Caucasian</td>
<td>28.5</td>
<td>7.2</td>
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<td>SCR02-0007</td>
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<td>Male</td>
<td>Caucasian</td>
<td>19.4</td>
<td>108.7</td>
<td>HD only</td>
<td>10.1</td>
<td>3/week</td>
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<tr>
<td>SCR02-0008</td>
<td>27</td>
<td>Female</td>
<td>Caucasian</td>
<td>22.7</td>
<td>296.6</td>
<td>HD only</td>
<td>23.2</td>
<td>3/week</td>
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<tr>
<td>SCR02-0010</td>
<td>29</td>
<td>Male</td>
<td>Caucasian</td>
<td>19.6</td>
<td>151.9</td>
<td>HD and PD</td>
<td>4.0</td>
<td>6/week</td>
</tr>
</tbody>
</table>

* Calculated as: date screening visit – earliest recorded dialysis + 1. b At baseline. PH = Primary hyperoxaluria; HD = hemodialysis, PD = Peritoneal dialysis.
Summary and Conclusions

- Primary Hyperoxaluria should be looked at in every patient with Ca-Ox stone disease
- Genetic Diagnosis is available for all three known types of PH
- Current Best Medical Rx is inadequate except for some homozygous Gly170→Arg mutation patients
- Liver Transplant is Curative, but requires lifelong immunosuppression and its consequences
- Early results of using siRNA removal of the final common pathway for oxalate overproduction (LHDA) is promising in patients with CKD and would avoid the need for organ transplantation if demonstrated as both safe and successful in longer-term studies of humans
- The OC5 product of O.formigenes may have some benefit in adult dialysis patients.
“Wait a minute here, Mr. Crumbley. ... Maybe it isn't kidney stones after all.”