Real-world disease manifestations and healthcare resource use (HRU) among patients with primary hyperoxaluria type 1 (PH1): a chart review study

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Disclosures

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David Danese and Tom Brown are employees of Alnylam Pharmaceuticals. Jessica Baldwin is a former employee of Alnylam Pharmaceuticals; she is currently an employee of Vertex Pharmaceuticals. Michael L Moritz and Xiangling Wang are consultants of Alnylam. Gautam Sajeev, Erin E Cook, Yao Wang, Chunyi Xu and Hongbo Yang are employees of Analysis Group Inc., which received funding for this research from Alnylam Pharmaceuticals.

Background and Objective

- Primary hyperoxaluria type 1 (PH1) is an ultra-rare, autosomal recessive, life-threatening disease that causes irreparable damage to the kidneys and other vital organs[1]
- The prevalence of PH1 is estimated to be 1-3 cases per 1,000,000 people in Europe and North America[1]
- Patients with PH1 have a deficiency in the AGT enzyme which results in excess hepatic oxalate production, which is excreted by the kidneys, resulting in a range of possible adverse clinical consequences
  - In the kidneys, the excess oxalate combines with calcium to form insoluble calcium oxalate (CaOx) crystals, which can result in kidney stones, nephrocalcinosis and progressive kidney damage, ultimately leading to kidney failure
  - The eventual loss of kidney function and inability of kidneys to fully clear oxalate can result in systemic oxalosis, in which oxalate accumulates in plasma and leads to extrarenal CaOx crystal formation, with resultant damage to bone, heart, skin, and / or eyes
- Current literature on the natural history of PH1 has typically focused on the outcomes of kidney failure and mortality; data on healthcare resource use (HRU) in PH1 is scarce [2-5]

Objective

This multi-country, retrospective, online chart review study was conducted to characterize the clinical and HRU burden of PH1 at various stages of kidney disease, with a focus on the burden of the disease prior to kidney failure

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[4] Hoppe B, Langman CB. A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. Pediatric Nephrology. 2003;18(10):986-991.
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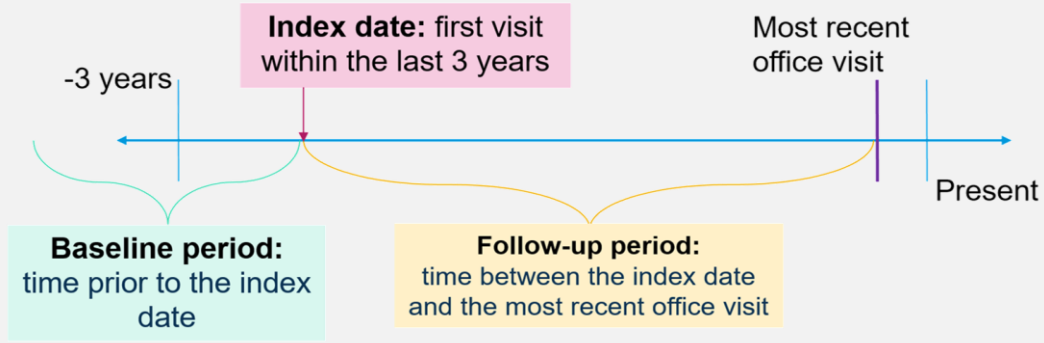
Methods

- An online, panel-based physician chart review study was conducted among adult and pediatric nephrologists in the US, Canada, UK, France, Germany and Italy
  - Nephrologists were recruited from the Schlesinger Group healthcare and partner panels, which are large online panels of over 125,000 physicians
- Participating nephrologists were asked to abstract chart data for up to 5 randomly selected patients who met the study eligibility criteria and enter this data into a standardized online questionnaire prepared by the investigators
- Data starting from the study index date (first visit in the last 3 years) were collected for each patient
- This study was approved by the New England IRB on October 17, 2019

Key analysis time points / time intervals



Physician eligibility criteria:

1. Practicing adult or pediatric nephrologist
2. Physician primarily responsible for the management of ≥1 patient's PH1
3. Have ≥1 PH1 patient who meets the patient inclusion criteria

Patient eligibility criteria

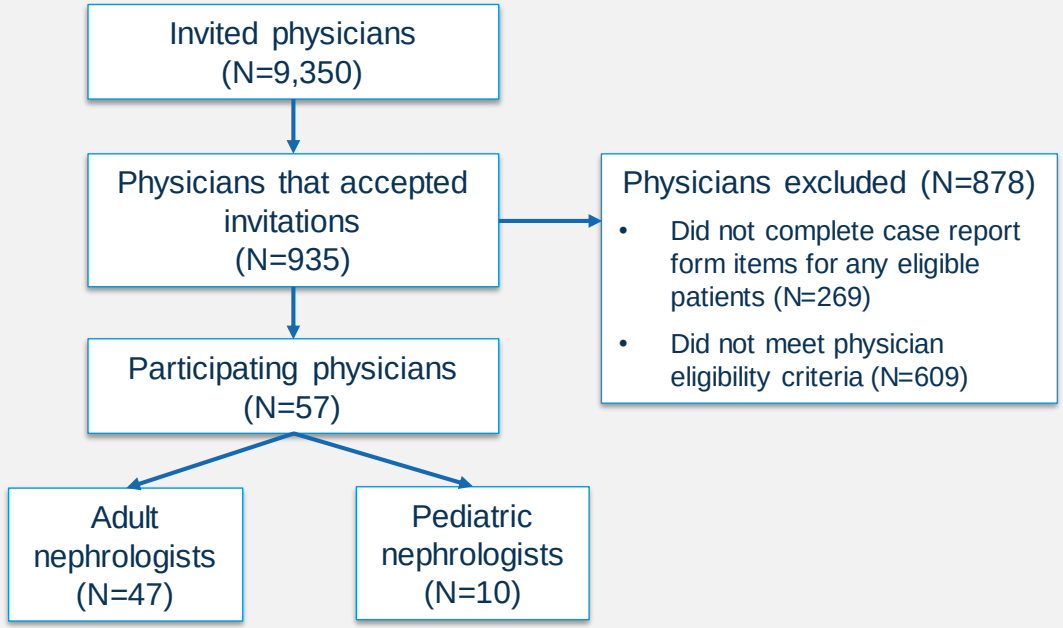
1. Patients with a confirmed diagnosis of PH1 by a positive genetic test or a positive liver biopsy-based AGT assay
2. Patients with ≥2 office visits to the participating physician within the last 3 years
3. Patients with the following information accessible in their charts since the fist visit that occurred within the last 3 years
   i. Signs, symptoms and clinical manifestations of PH1
   ii. PH1-related HRU (e.g., number of hospitalizations)

Results

Physician recruitment and characteristics

- 57 physicians meeting the study eligibility criteria provided information on 120 eligible patients with PH1
- Approximately one-third of participating nephrologists were based in the United States, with smaller proportions in France, Italy, the United Kingdom, Canada, and Germany
- All participating physicians were nephrologists, including 17.5% who were pediatric nephrologists.

Recruitment of physicians participating in chart review study



Country of origin for participating physicians and patients

Country	Number of Physicians	Number of Patients
Total	***57***	***120***
US	19	37
UK	8	18
Canada	7	16
France	10	19
Germany	5	15
Italy	8	15

Results

Patient characteristics at PH1 diagnosis and index

- At diagnosis: Median patient age (N=82) was 17.4 years (Interquartile range [IQR]: 11.1, 24.9); of those with available eGFR data (N=86), 15.1% had eGFR ≥90 ml/min/1.73m2, 33.7% had eGFR 60-<90, and 41.9% had eGFR 30-<60
- At index date: Median patient age (N=99) was 19.5 years (IQR: 15.7, 28.7); of those with available eGFR data (N=81), 13.6% had eGFR ≥90 ml/min/1.73m2, 23.5% had eGFR 60-<90, and 42.0% had eGFR 30-<60
- Median duration of post-index follow-up was 1.7 years

Patient demographic characteristics

Characteristic	Value
Age at index, median (IQR), years (N=99)	19.5 (15.7, 28.7)
n (%) 0 - <2 years	3 (3.0%)
n (%) 2 - <6 years	2 (2.0%)
n (%) 6 - <18 years	36 (36.4%)
n (%) ≥18 years	58 (58.6%)
Gender (N=118)	
n (%) female	42 (35.6%)
n (%) male	76 (64.4%)
Race (N=119)	
n (%) White or Caucasian	93 (78.2%)
n (%) Black	12 (10.1%)
n (%) Asian	10 (8.4%)
n (%) Other	4 (3.4%)

Patient clinical characteristics

Characteristic	Value
Years from diagnosis to index, median (IQR), (N=62)	1.1 (0.2, 5.9)
eGFR at index, median (N=81), ml/min/1.73^2	45.0 (35.0, 75.0)
n (%) eGFR ≥ 90 mL/min/1.73m^2	11 (13.6%)
n (%) eGFR 60-89 mL/min/1.73m^2	19 (23.5%)
n (%) eGFR 30-59 mL/min/1.73m^2	34 (42.0%)
n (%) eGFR 15-29 mL/min/1.73m^2	10 (12.3%)
n (%) eGFR <15 mL/min/1.73m^2	7 (8.6%)
Treatment history (past or current) at index (N=111)	
n (%) hyperhydration	78 (70.3%)
n (%) crystallization inhibitors	67 (60.4%)
n (%) pyridoxine	45 (40.5%)

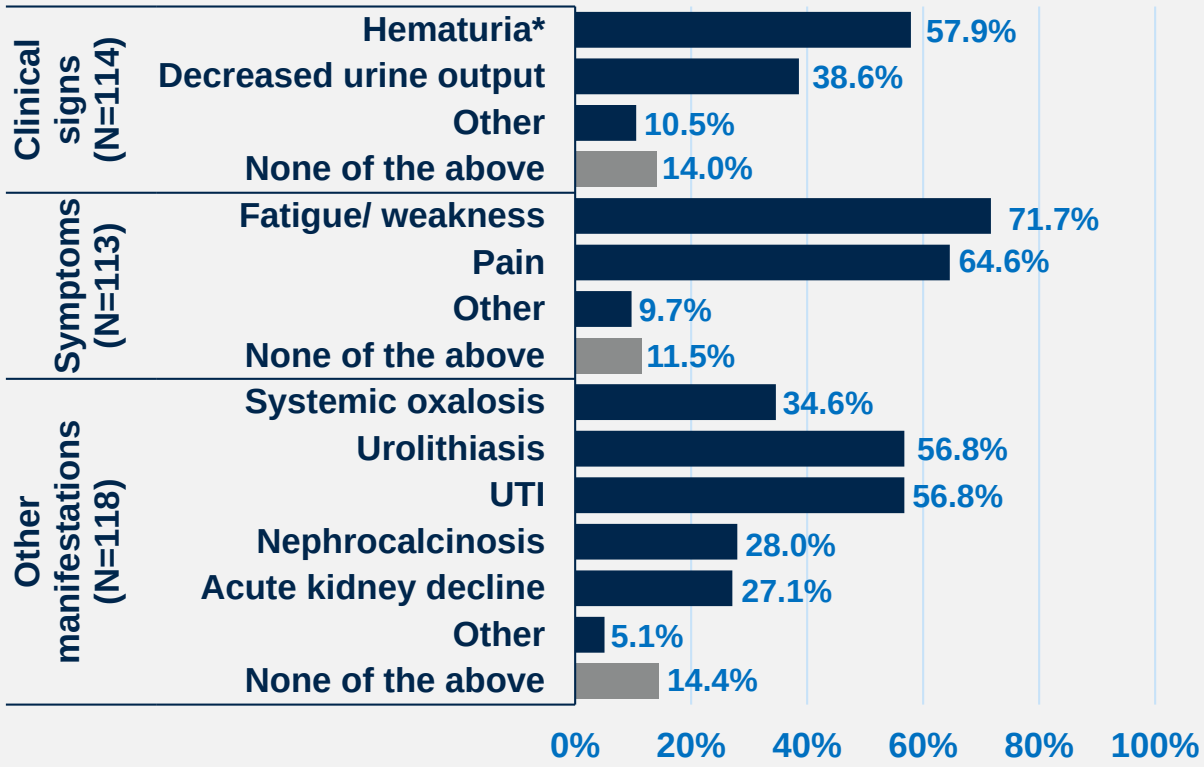
N represents sample size contributing data

Results

Disease manifestations during follow-up

- During the follow-up period, the most common signs and symptoms of PH1 were fatigue / weakness (71.7%), pain (64.6%), and hematuria (57.9%)
- Other commonly observed manifestations included various forms of systemic involvement (34.6%), urolithiasis (56.8%), UTI (56.8%), nephrocalcinosis (28.0%), and acute kidney decline (27.1%)
  - Clinically evident stone events and UTIs (the most common acute manifestations of PH1) were reported at incidence rates of 0.8 per patient-year (PY) and 1.0 per PY, respectively
  - Most common systemic manifestations of PH1 included anemia, arrhythmias, and bone pain
  - Most common causes of acute kidney decline included dehydration, infection, and obstructive stone events

Prevalence of clinical signs, symptoms and other PH1 manifestations during follow-up



*Defined per data collection form as “blood in urine”
Note: Acute kidney decline was defined as an acute eGFR decline by 20% or more
N represents number of patients contributing data

Results

Late-stage outcomes

- At the time of data collection, approximately one-fifth of patients (20.4%) ever had kidney failure (captured as “end-stage renal disease” in the data collection form)
  - Among patients affected, kidney failure occurred at a median age of 25.3 years
- At the time of data collection, 8.2% of patients in the analysis population were deceased
  - Among deceased patients, median age at death was 35.0 years

Late-stage outcomes of PH1: Kidney failure* and death

Late-stage outcomes (n contributing data)	Value
Patients that ever had kidney failure (N=113)	23 (20.4%)
Median (IQR) age at diagnosis of kidney failure, years (N=16)	25.3 (20.5, 34.2)
Diagnosis of kidney failure relative to PH1 diagnosis (N=23)	
n (%) diagnosis of kidney failure at or after PH1 diagnosis	11 (47.8%)
n (%) diagnosis of kidney failure before PH1 diagnosis	3 (13.0%)
n (%) unknown	9 (39.1%)
Deceased on survey date (N=110)	9 (8.2%)
Median (IQR) age at death, years (N=5)	35.0 (21.0, 35.0)

*Captured as “end-stage renal disease,” which was defined as being in CKD stage 5 with need for dialysis

Results

HRU during follow-up

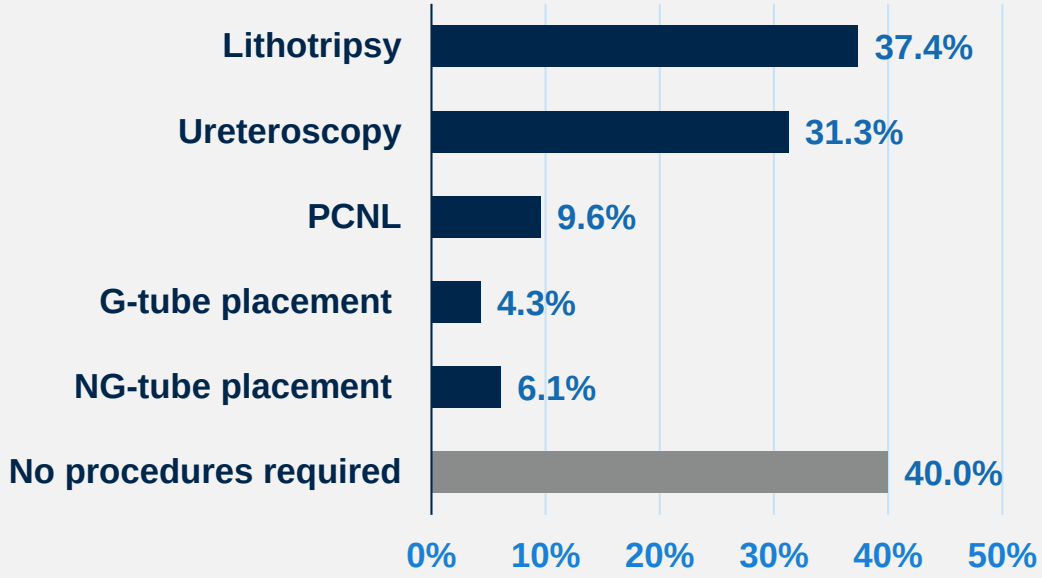
- During follow-up, most patients required a PH1-related hospitalization and / or emergency care visit
  - Hospitalizations and emergency visits each occurred at a rate of 1.1 per PY
- During follow-up, approximately one-third of patients had ≥1 lithotripsy and approximately one-third had ≥1 ureteroscopy to manage kidney stones during follow-up, while 9.6% had ≥1 percutaneous nephrolithotomy (PCNL)
  - Patients with ≥1 lithotripsy required lithotripsy procedures at a rate of 1.2 per PY; corresponding rates for patients with ≥1 ureteroscopy and ≥1 PCNL were 1.0 and 0.6 procedures per PY, respectively

PH1-related healthcare visits during follow-up

Variable	Value
Hospitalizations (N=94)	
n (%) of patients with ≥1 during follow-up	79 (84.0%)
Total number during follow-up	167
Incidence rate	1.1 per patient-year
Median length of stay (IQR), days	5.0 days (3.0, 7.5)
Urgent or emergency care visits (N=87)	
n (%) of patients with ≥1 during follow-up	71 (81.6%)
Total number during follow-up	161
Incidence rate	1.1 per patient-year
Outpatient visits (N=89)	
n (%) of patients with ≥1 during follow-up	87 (97.8%)
Total number during follow-up	589
Incidence rate	4.0 per patient-year

N represents sample size contributing data

Percentage of patients with PH1 requiring specified medical procedures during follow-up



G-tube: gastrostomy tube; NG-tube: nasogastric tube
Note: Data are among 115 patients with known information on procedures

Discussion and conclusions

- Study aim: Better characterize clinical/HRU burden across disease stages in patients with PH1, most without kidney failure
  - Prior reports provide limited data on clinical outcomes of PH1 before kidney failure and mortality, and data on HRU in PH1 is scarce[2-5]
- Patients in this study were found to have high clinical and HRU burden
  - Many patients experience adverse clinical consequences, including pain, fatigue, stone events, and UTIs
  - Although preliminary in nature, selected findings suggest other clinical manifestations (e.g., acute kidney decline, certain systemic manifestations) may be additional, underappreciated elements of clinical burden and warrant further exploration
  - Stone procedures were common (annual to biannual), and >80% of patients had ≥1 hospitalization and/or emergency visit during follow-up
- The observed clinical and HRU burden of PH1 were present despite the fact that this cohort included fewer patients with eGFR <15 mL/min/1.73m^2 at diagnosis than other published cohorts[2,3,6]
- Findings should be interpreted in view of the following methodological considerations
  - This study includes fewer pediatric patients compared to previous PH1 studies, due to lower participation of pediatric nephrologists
  - The study questionnaire may have been challenging to complete due to its comprehensive and detailed nature, which may have impacted data quality and completeness, particularly for clinical and HRU event counts
  - Findings on acute decline in kidney function and systemic manifestations of PH1 are preliminary and should be interpreted with caution, due to potential ambiguity regarding event definitions and clinical significance

Conclusion

The current study highlights an ever-present risk of ongoing morbidity and significant HRU, which accompany the ongoing risk of progressive kidney decline in PH1 and underscore the urgent need for effective treatment of PH1 throughout the disease course

[6] Danpure CJ, Jennings PR. Peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type I. FEBS Letters. 1986;201(1):20-34.