Natural History of Advanced Primary Hyperoxaluria Type 1: A Retrospective Study

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Conclusions

- **Advanced PH1 is associated with high morbidity and mortality; liver and/or kidney transplantation have frequently been pursued**
- **Although liver transplantation corrects the metabolic defect, it may also carry significant risk**
- **The rate of eGFR decline in this study was slower than that observed in patients with PH1 and chronic kidney disease (stage 3a, 3b, or 4) in a recent retrospective observational study[1]**
  - **However, the required minimum amount of follow-up for eligible patients (≥4 healthcare visits related to PH1 spanning ≥6 months) may have been a source of bias**
- **The novel bone oxalosis grading scale employed in this study shows, in general, worsening of oxalosis in the pre-transplant period and slow improvement post-transplant**
- **Low bicarbonate levels occurred in nearly all patients in the non-dialysis cohort and most patients in the hemodialysis cohort**

Introduction

- PH1 is a genetic disease of oxalate overproduction that can cause progressive kidney damage and systemic oxalosis[2]
- Systemic oxalosis can involve multiple organs, including the bones and heart[3]
- When kidney function is severely compromised in PH1, one or more of the following may be required: dialysis, kidney transplant, or combined liver-kidney transplant[4,5]
- We aimed to characterize the natural history of PH1 in patients with advanced renal impairment and elevated POx or systemic oxalosis, or who require dialysis, in the context of standard of care

Methods

- In this retrospective, multinational chart review study, eligible patients had ≥4 healthcare visits related to PH1 spanning ≥6 months (except deceased patients) on or after January 1, 2000, and ≥2 eGFR values ≤45 mL/min/1.73m^2 (or, if age <12 months, 2 serum creatinine values elevated for age [>ULN])
  - Diagnosis details, laboratory values, clinical events, and imaging data were collected through August 17, 2022
- Patients were assigned to one or both of 2 cohorts: Cohort A (nondialysis) and Cohort B (on hemodialysis for ≥4 weeks without peritoneal dialysis)
  - Patients could be in more than 1 cohort, but not during the same time period
- The full analysis set includes all patients who met the eligibility criteria for the study; the POx analysis set includes all patients in the full analysis set who had ≥1 POx measurement on or after the date that the cohort criteria were met and a second POx measurement ≥82 days later, without a censoring event
- Censoring events included participation in a therapeutic clinical trial, initiation of lumasiran, liver and/or kidney transplant, and initiation of peritoneal dialysis

Results

- In total, 70 patients were analyzed with up to 21 years of data
- Fifty-four patients met criteria for Cohort A, 53 met criteria for Cohort B, and 37 met criteria for both (**Table 1**)
- The POx analysis set included 11 patients in Cohort A, 11 in Cohort B, and 1 in both cohorts
  - POx values were generally elevated at baseline, and almost always higher in Cohort B than in Cohort A; neither cohort showed evidence of an annual POx reduction (no change was suggested by the 95% CI)

Table 1. Baseline Characteristics

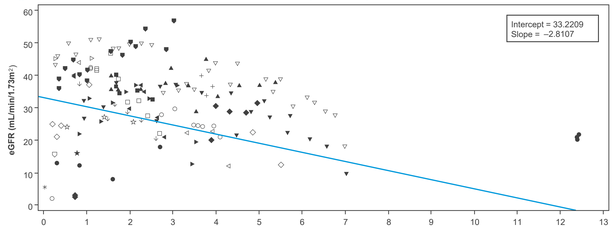
Characteristic	Full Analysis Set[a] (N=70)	
	Cohort A[b] (N=54)	Cohort B[b] (N=53)
Age at Day 1, median (min, max), years	11.8 (0, 57)	12.2 (0, 58)
Female, n (%)	27 (50)	26 (49)
Race, n (%)		
White	41 (76)	40 (75)
Asian	1 (2)	0
Other/not reported/unknown	12 (22)	13 (25)
Time from diagnosis to Day 1, median (min, max), months[c]	−0.1 (−42, 383)	4.6 (−30, 432)
eGFR, median (min, max), mL/min/1.73m^2	21.1 (1, 51)	N/A
Use of pyridoxine within 120 days prior to Day 1, n (%)	7 (13)	13 (25)
Genotype[d], n (%)		
PR/*	21 (39)	20 (38)
M/M or M/N	14 (26)	9 (17)
N/N	14 (26)	19 (36)
Missing	5 (9)	5 (9)

[a]Includes all patients who met the eligibility criteria for the study. [b]Patients could be in more than 1 cohort, but not during the same time period. [c]Twenty-eight patients (Cohort A) and 13 patients (Cohort B) met cohort entry criteria prior to PH1 diagnosis. [d]PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). M and N were defined based on a publication by Mandrile et al.[6] The asterisk (*) denotes any genotype of PR, M, or N. M, missense; N, nonsense; PR, pyridoxine-responsive.

- In Cohort A, eGFR slope was −2.8 mL/min/1.73m^2/y (**Figure 1**)
- In Cohort B, patients underwent hemodialysis a median of 6 days/week (range 3–7; N=41) and 3.8 hours/session (range, 2–8; N=31). The median frequency and duration of hemodialysis sessions did not change meaningfully over the 4 years of data collection

Results (cont'd)

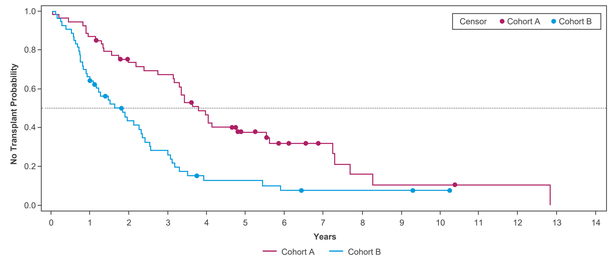
Figure 1. Model of Actual eGFR Values Over Time (Cohort A)[a-c]



[a]Full analysis set. [b]25 patients contributed to the slope. [c]eGFR was calculated from serum creatinine based on the Schwartz Bedside Formula for patients ≥12 months to <18 years of age, and the Modification of Diet in Renal Disease Formula for patients ≥18 years of age. A formula for calculating eGFR has not been validated for children <12 months of age with chronic kidney disease; therefore, eGFR is not presented for this age range.

- Forty-two patients underwent liver and/or kidney transplantation at least once (Cohort A [32/54], Cohort B [36/53], or both [42/70])
  - The median age at first transplant was 15.3 years
  - The majority of patients had a dual or sequential liver-kidney transplant; 2 patients had a kidney transplant; and 3 patients had a liver transplant
  - Median time from Day 1 to first organ transplant was 4.03 years in Cohort A and 1.89 years in Cohort B (**Figure 2**)

Figure 2. Time to First Organ (Liver and/or Kidney) Transplant[a]



Note: One patient in Cohort A was deceased (unknown year of death). Patients without an event are censored at the last known date they were alive.
[a]Full analysis set; organ transplants were censored only if a patient participated in a clinical trial or initiated lumasiran.

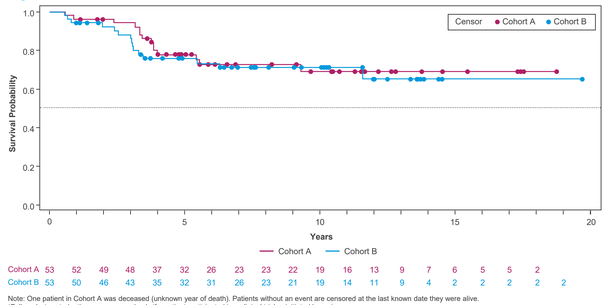
- Nineteen of 70 patients died (date of death was not provided for 1 patient)
  - The median age at death was 3.9 years (range, 2.2–34.9); systemic oxalosis was evident in all
- Of the 19 patients who died, 8 had received a liver transplant or liver-kidney transplant (sequential or dual) (**Table 2**)
  - Among these, the primary cause of death was transplant-related in 3 patients, all of whom died within 6 months of transplant; an additional 2 patients died within 6 months of transplant, but the primary cause of death was not considered to be transplant-related

Table 2. Deaths and Transplants Among Patients Who Died

Patient	Sex	Date of Death (Month/Year)	Age at Death (Years)	Primary Cause of Death	Transplant	Date of Transplant (Month/Year)
1	F	April 2020	34.9	Unknown		
2	M	August 2014	27.2	Unknown	Dual liver-kidney	May 2012
					Dual liver-kidney	August 2014
3	F	November 2010	3.6	Sepsis		
4	M	September 2019	6.1	Systemic oxalosis		
5	M	December 2018	3.7	Respiratory failure		
6	M	February 2018	6.7	Septic shock	Liver	September 2017
7	F	December 2014	2.2	Septic shock		
8	M	November 2016	2.3	Unknown		
9	F	October 2015	3.0	Unknown		
10	F	June 2011	4.0	Cardiac arrest		
11	F	Not reported	Not reported	Unknown		
12	F	August 2016	12.7	Unknown	Liver	May 2007
					Kidney	July 2007
13	F	July 2014	2.8	PH1		
14	M	July 2017	3.5	Liver transplant surgery	Liver	July 2017
15	F	June 2017	5.8	PH1	Liver	September 2013
					Kidney	July 2015
16	M	January 2017	3.7	PH1		
17	M	May 2011	3.8	PH1	Liver	April 2010
18	F	September 2009	4.2	Dual liver-kidney transplant	Dual liver-kidney	September 2009
19	F	July 2017	15.2	Liver graft failure	Dual liver-kidney	May 2017

- Median time from Day 1 to death in patients who died was 3.6 years in Cohort A and 3.0 years in Cohort B (**Table 2**)

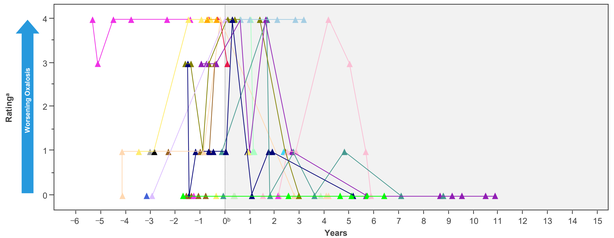
Figure 3. Time to Death[a]



Note: One patient in Cohort A was deceased (unknown year of death). Patients without an event are censored at the last known date they were alive.
[a]Full analysis set; deaths were censored only if a patient participated in a clinical trial or initiated lumasiran.

- There was a trend toward worsening in skeletal oxalosis grade before first organ transplant and improvement after first organ transplant
  - Skeletal oxalosis grade improvement after liver-kidney transplantation generally took more than a year (**Figure 4**)
- Limited echocardiogram data were available (Cohort A, N=7; Cohort B, N=9): LVEF was normal except for 1 patient in Cohort A with persistently low LVEF <50% (range 35%-45%), and 1 patient in Cohort A who was low at one time point (range 46%-60%)

Figure 4. Representative Figure of Skeletal Oxalosis Grade Improvement: Left Humerus in Individual Patients (N=25) After the First Liver and/or Kidney Transplant



Note: Each colored line represents an individual patient.
*Bone x-ray images were evaluated centrally for evidence of systemic oxalosis and graded using a novel bone oxalosis grading scale.[7] The skeletal systemic oxalosis questions were rated as a 0 to 4 (most severe oxalosis) for the left humerus. †Time 0 represents time of the first transplant; shading indicates post-transplant scores.

- The most common emergent clinical events were nephrolithiasis (Cohort A) and fracture (Cohort B) (**Table 3**)
  - Four events of nephrolithiasis were reported for 3 (6%) patients in Cohort A, and 14 events of fracture were reported for 6 (11%) patients in Cohort B
  - Exposure-adjusted incidence rates of clinical events requiring hospitalization were higher in Cohort B than in Cohort A (71.6 versus 5.9 per 100 PY)

Table 3. Summary of Emergent Clinical Events[a,b]

Category	Cohort A (N=54, PY=101)		Cohort B (N=53, PY=90.8)	
	N (%)	ER	N (%)	ER
At least 1 emergent clinical event	10 (19)	29.7	29 (55)	133.3
At least 1 PH1-related emergent clinical event	6 (11)	13.9	16 (30)	35.2
At least 1 non–PH1-related emergent clinical event	5 (9)	14.9	21 (40)	89.2
At least 1 emergent clinical event resulting in hospitalization	6 (11)	5.9	20 (38)	71.6

Note: ER = exposure-adjusted incidence rate per 100 patient years (PY).
[a]Full analysis set. [b]Defined as clinical events that occurred or worsened on/after Day 1.

- The most commonly reported abnormal clinical laboratory values were bicarbonate, creatinine, and eGFR
  - In Cohort A, out of 21 patients with available bicarbonate data, 20 (95%) had at least one low bicarbonate value, 2 (10%) had high bicarbonate values, and 1 (5%) had both high and low values
  - In Cohort B, out of 23 patients with available bicarbonate data, 17 (74%) had at least one low bicarbonate value, 10 (44%) had high bicarbonate values, and 4 (17%) had both high and low values

Abbreviations: BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; ER, exposure-adjusted incidence rate per 100 patient-years; LVEF, left ventricular ejection fraction; M, month; PH1, primary hyperoxaluria; PY, patient-years; SEM, standard error of the mean; ULN, upper limit of normal.

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