Kidney Survival in Patients with Primary Hyperoxaluria Type 1 Treated with Lumasiran Compared with Historical Controls

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Abstract

BACKGROUND
Primary hyperoxaluria 1 (PH1) is associated with a high risk of kidney failure due to increased hepatic production and urinary excretion of oxalate. Clinical trials confirm that the novel small inhibitory RNA lumasiran can reduce urinary oxalate excretion (UOX) in adult and pediatric PH1 patients with and without preexisting chronic kidney disease (CKD). In order to estimate the potential magnitude of kidney failure reduction and changes in UOX and eGFR over follow-up, we compared lumasiran treated PH1 patients to a control cohort of historical standard of care patients not receiving this drug from the rare kidney stone consortium (RKSC) registry.

METHODS
PH1 patients from the ILLUMINATE-A trial administered lumasiran comprised the treated cohort. PH1 patients from the RKSC registry satisfying similar inclusion criteria (aged ≥6 years, eGFR ≥30 mL/min/1.73 m^2, with UOX ≥0.7 mmol/1.73m^2/24hr and follow-up available) were identified as the standard of care control cohort. Inverse probability of treatment weighting (IPTW) using propensity scores was used to estimate the effect of lumasiran on kidney survival, UOX and eGFR, and included the baseline variables age, sex, UOX, eGFR, and age at PH1 diagnosis. Weighted Cox proportional hazards regression evaluated the association between treatment group and time to incident kidney failure or death. Weighted linear regression analyses were used to assess the associations between treatment group and follow-up UOX and eGFR.

RESULTS
In the weighted sample, patient characteristics were well balanced. Estimated kidney survival at 4 years was 88% (82%-94%) in the RKSC cohort and 100% (91%-100%) in the lumasiran cohort. Lumasiran treatment was associated with a reduced kidney failure or death hazard compared to historical standard of care patients (HR (95% CI): 0.049 (0.031, 0.094), P<0.001). Annual rate of eGFR decline was slower in lumasiran patients compared with standard of care patients (mean (SD) annual rate of change: -1.51 (6.09) mL/min/1.73m^2/year vs -6.27 (19.2), respectively), and estimated 5 year follow-up UOX levels were lower in lumasiran patients vs standard of care patients (0.84 (95% CI: 0.70 to 0.99) mmol/1.73m^2/24hr vs 1.54 (1.26 to 1.79), respectively).

CONCLUSIONS
Our study suggests a clinically meaningful improvement in kidney survival after lumasiran treatment.

Objectives

We propose using historical patients from a well-established PH1 patient disease registry using standard of care treatment at the time as controls to compare with patients from the ILLUMINATE-A trial who were all administered lumasiran treatment (approved as an effective treatment for PH1 patients to lower oxalate) after 6 months post-RCT and were followed up for 5 years for follow-up outcomes, including kidney survival, UOX, and eGFR.

Patient Cohort and Methods

LUMASIRAN TREATED PATIENTS
In the ILLUMINATE-A trial, 39 patients with PH1 were randomized 2:1 to receive lumasiran or placebo. After 6 months follow-up, all patients received lumasiran in an open-label extension. Patients included in the trial were ages 6 years or older, had a 24-hr BSA-corrected UOX of 0.7 or higher, and had an eGFR of 30 or higher.

RKSC STANDARD OF CARE PATIENTS
116 PH1 patients from the RKSC retrospective registry free of kidney failure at diagnosis who would have met inclusion criteria for the ILLUMINATE trial who were receiving standard of care were included in the cohort. Baseline was defined as the 1st available UOX measure that met the following criteria: age 6 years or older, eGFR 30 or higher, a 24-hr BSA-corrected UOX of 0.7 or higher, and follow-up available at least 1 month after baseline. The range of baseline dates for patients in the RKSC cohort were 1969-2023 (n=27 (23.3%) prior to 2000, n=52 (44.8%) between 2000-2010, and n=37 (31.9%) after 2010).

STATISTICAL ANALYSIS
Regression models were weighted by inverse probability of treatment weighting (IPTW) using propensity scores. Baseline variables included in the propensity model were: age, sex, BSA-corrected UOX, eGFR, and age at PH diagnosis. Kidney survival estimates and 95% confidence intervals during 5 years of follow-up were derived using Nelson-Aalen estimators. Hazard ratios comparing the lumasiran treated vs standard of care groups were estimated using weighted cox proportional hazards regression with the Firth correction, and 95% confidence intervals and P-values were derived using bootstrapping. 5-year follow-up UOX estimates were derived from linear mixed regression modeling using a restricted cubic spline term, and standardized area under the curve (AUC) estimates were calculated for each patient using the trapezoidal method. Annual absolute rate of change of eGFR over 5 years was calculated for each patient using the least squares slope of eGFR regressed on time. Weighted linear regression analyses were used to predict AUC and annual rate of change in eGFR from treatment group.

Table 1. Baseline patient characteristics included in the propensity score model of lumasiran treated and RKSC Standard of Care patients, before and after IPTW

	Before IPTW			After IPTW		
Baseline Characteristic	lumasiran treated patients (N=39)	RKSC historical controls (N=116)	SMD	lumasiran treated patients (N=39)	RKSC historical controls (N=116)	SMD
Age, mean (SD)	18.1 (12.7)	19.7 (14.2)	-0.115	22.2 (17.1)	19.7 (14.5)	0.184
Female sex, %	33.3%	44.8%	-0.237	39.5%	42.0%	-0.052
UOX (mmol/1.73m^2/24hr), mean (SD)	1.77 (0.62)	1.68 (0.89)	0.115	1.80 (0.63)	1.70 (0.90)	0.138
eGFR (mL/min/1.73 m^2), mean (SD)	81.6 (26.8)	76.9 (25.4)	0.182	76.2 (28.1)	78.1 (25.9)	-0.071
Age at PH1 Diagnosis, mean (SD)	8.8 (11.6)	14.7 (14.1)	-0.456	16.0 (18.7)	13.4 (13.3)	0.200

Standardized mean differences (SMD) of <0.2 generally indicate good covariate balance between groups.

Figure 1. Kidney survival curve during 5 years of follow-up, by treatment cohort

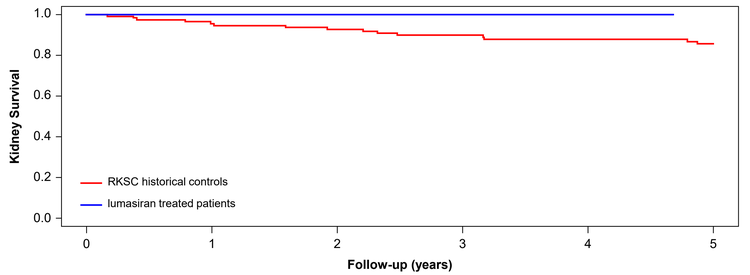


Table 2. Kidney survival estimates (95% CI) during 5 years of follow-up, by treatment cohort

	Kidney Survival (95% CI)		
Follow-up Time	1 year	2 years	4 years
RKSC historical controls*	96% (92%-99%)	93% (88%-98%)	88% (82%-94%)
lumasiran treated patients†	100% (91%-100%)	100% (91%-100%)	100% (91%-100%)

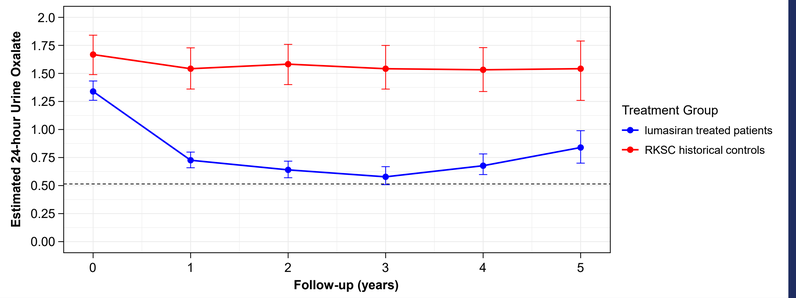
*95% confidence intervals calculated using Greenwood's formula
†95% confidence intervals calculated using Clopper-Pearson's formula due to no events occurring in the lumasiran group.

Table 3. eGFR annual rates of absolute change up to 5 years follow-up, by treatment cohort

				Annual rate of change over 5 years (mL/min/1.73m^2/year)		
Treatment Group	N*	N eGFR	N follow-up eGFR per patient, Median [IQR]	Mean (SD)	Median [IQR]	P**
lumasiran treated patients	38	715	21 [15, 22]	-1.51 (6.09)	-0.52 [-2.09, 0.90]	0.13
RKSC historical controls	101	469	4 [3, 6]	-6.27 (19.2)	-1.76 [-6.98, 1.07]	**0.001**

**P-values derived using the 1 sample t-test.
Unequal variance 2-sample test comparing annual rate of change over 5 years between two treatment groups: P=0.029

Figure 2. Average (95% CI) estimated 24-hour UOX across 5 years of follow-up, by treatment group. Dashed line represents Upper limit of normal for UOX.



Results

In weighted analyses adjusting for IPTW, compared to RKSC standard of care patients, lumasiran treated patients:
- Had a significantly lower risk of kidney failure or death: HR (95% CI): 0.049 (0.031, 0.094), P<0.001.
- Achieved significantly lower levels of follow-up UOX over 5 years as measured by the standardized AUC: least squares mean difference (95% CI): -0.88 (-1.08, -0.67), P<0.001.
- Had a significantly slower annual rate of eGFR decline over 5 years (least squares mean difference (95% CI): 5.31 (0.88, 9.74), P=0.019.

Conclusions

These results suggest that long-term treatment with lumasiran provides a clinically meaningful improvement in kidney survival in PH1 patients compared to the observed natural history of progression in historical standard of care patients.

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