Lumasiran: Use in Kidney Transplantation

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SUMMARY

- In the lumasiran phase 3 clinical trials, patients who received a prior KT and/or immunosuppressants at the time of study initiation were excluded from the ILLUMINATE studies.[1–3]
- In the ILLUMINATE-C trial, patients with advanced kidney disease were included in the study. As of Month 36 of the extension period, there were 5 patients that received isolated KT and continued lumasiran treatment post-transplant.[3,4]
- Case reports from published medical literature discuss the use of lumasiran in patients with PH1 who have had an isolated KT.[5–11]

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ILLUMINATE-C

ILLUMINATE-C was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by an ongoing 54-month extension period to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in full term infants to adult patients with advanced PH1 with an eGFR ≤45 mL/min/1.73m^2 (or elevated serum creatinine if <12 months old) and POx ≥20 µmol/L. Patients enrolled in the study included those not receiving hemodialysis in Cohort A (N=6) and those receiving hemodialysis in Cohort B (N=15). Patients received subcutaneous injections of lumasiran as determined by a body weight-based dosing regimen. The primary endpoints were the percent change from baseline in POx at 6 months (Cohort A) and percent change from baseline in predialysis POx at 6 months (Cohort B).[12]

Patients were excluded from the study if any of the following criteria applied:[3]

- Had a previous liver transplant or a liver transplant was anticipated within the next 6 months of the study
- Had a previous KT and were currently receiving immunosuppression to prevent transplant rejection.

Patient Demographics & Baseline Characteristics

A total of 21 patients were enrolled (6 in Cohort A and 15 in Cohort B). All patients completed the 6-month primary analysis period and entered the extension period. Relevant baseline characteristics are described in **Table 1**.[12]

Table 1. Select Baseline Characteristics.[12]

Baseline Characteristic	Cohort A (N=6)	Cohort B (N=15)	All Treated (N=21)
Median age at consent (range), years	9 (0-40)	6 (1-59)	8 (0-59)
Plasma oxalate[a], median (range) µmol/L	57.9 (22.7-134.0)	103.7 (56.3-167.0)	100.9 (22.7-167.0)
eGFR[b], median (range), mL/min/1.73 m^2	N=5 16.5 (8.6-34.1)	NA	N=5 16.5 (8.6-34.1)
Number of dialysis sessions per week, median (range)	NA	6 (3-7)	NA

Abbreviations: eGFR = estimated glomerular filtration rate; NA = not applicable.
[a]Upper limit of normal = 12.11 µmol/L (1.09 mg/mL) as determined based on data from 75 healthy adults.
[b]eGFR value was available for 5 patients in Cohort A. eGFR was calculated with the Modification of Diet in Renal Disease Study equation for those aged ≥18 years and the Schwartz bedside formula for those aged 1 to <18 years.

Isolated Kidney Transplantation Data

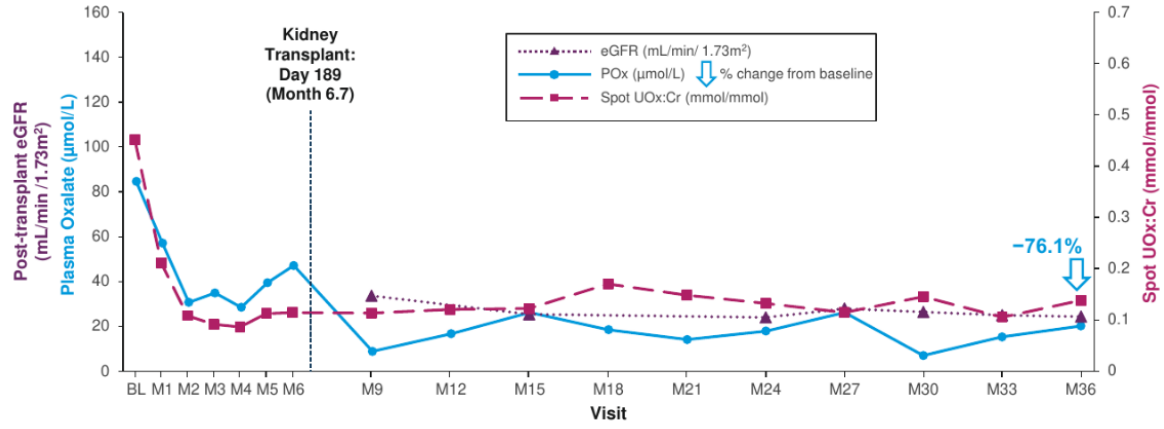
Of the 15 patients enrolled in Cohort B (on hemodialysis at study start), 5 patients underwent isolated KT as of Month 36 (**Figures 1-5**). Transplant decisions were made at the clinical discretion of the individual investigators.[4]

The baseline POx values of the 5 patients ranged from 84.6 to 152.3 µmol/L. Prior to KT, all 5 patients experienced reductions in POx from baseline ranging from -37.5 to -87.8 µmol/L. Further reductions post-transplant indicated improved POx clearance with functioning kidney grafts.[4]

Patient 1

Patient 1 was 44 years of age at the time of study entry and had a pyridoxine-responsive genotype. The patient received a KT on Study Day 189 (Month 6.7). The percent reduction from baseline in POx was 76.1% at Month 36 (**Figure 1**).[4]

Figure 1. Patient 1: POx, UOx:Cr, and Post-transplant eGFR through Month 36.[4]



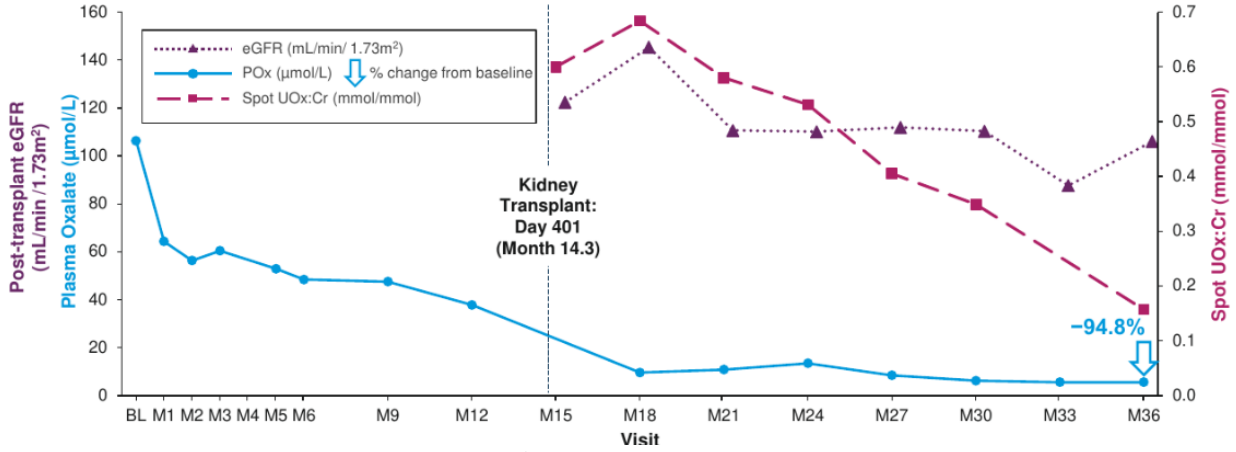
Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; POx = plasma oxalate; UOx:Cr = urinary oxalate:creatinine ratio.
From Somers et al.[4]

Patient 1 experienced a post-transplant AE of graft failure, which resolved. A renal graft biopsy performed 6 weeks after KT associated with this AE demonstrated evidence of BK virus nephropathy without calcium oxalate nephropathy.[4]

Patient 2

Patient 2 was 2 years of age at the time of study entry and had a non-pyridoxine-responsive genotype. The patient received a KT on Study Day 401 (Month 14.3). The percent reduction from baseline in POx was 94.8% at Month 36. (**Figure 2**).[4]

Figure 2. Patient 2: POx, UOx:Cr, and Post-transplant eGFR through Month 36.[4]



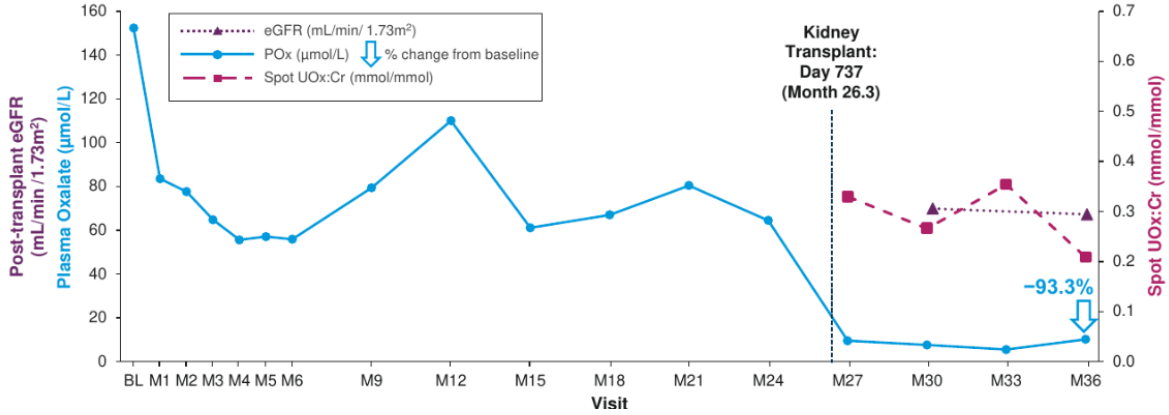
Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; POx = plasma oxalate; UOx:Cr = urinary oxalate:creatinine ratio.
From Somers et al.[4]

HD was stopped 36 days following KT. The reason for continuation of dialysis after KT was not reported. However, within the first month post-transplant, the patient experienced severe AEs of pyrexia 13 days after transplant; graft complication, urinoma, and AKI 14 days after transplant; and herpes simplex infection 21 days after transplant. The AEs were considered not related to lumasiran.[4]

Patient 3

Patient 3 was 0.9 years of age at the time of study entry and had a non-pyridoxine-responsive genotype. The patient received a KT on Study Day 737 (Month 26.3). The percent reduction from baseline in POx was 93.3% at Month 36. (**Figure 3**).[4]

Figure 3. Patient 3: POx, UOx:Cr, and Post-transplant eGFR through Month 36.[4]



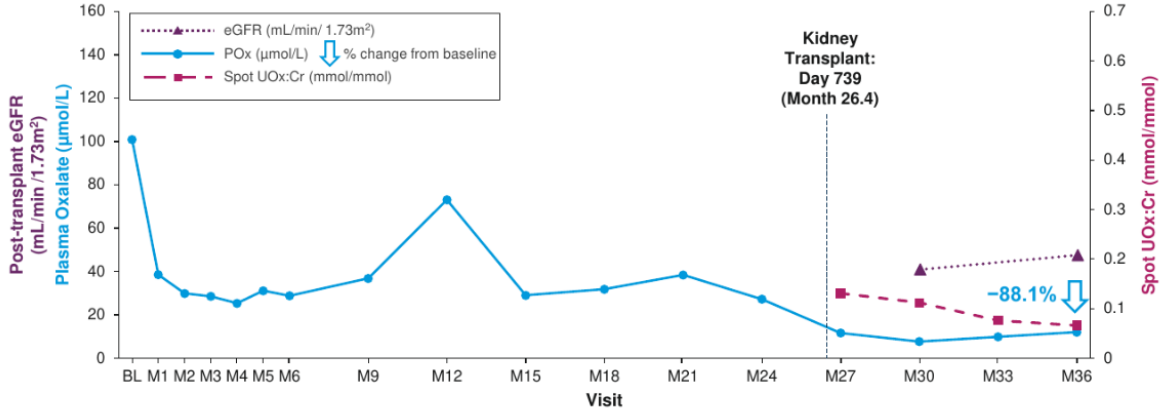
Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; POx = plasma oxalate; UOx:Cr = urinary oxalate:creatinine ratio.
From Somers et al.[4]

Patient 3 experienced a mild AE of UTI 14 days after transplant and recovered from the event. The AE was considered not related to lumasiran. Other complications that occurred within 3 months to 1 year after transplant and required hospitalization included a moderate AE of hypogammaglobulinemia; severe AEs of gastroenteritis, pneumonia, post-transplant lymphoproliferative disorder; and ear infection.[4]

Patient 4

Patient 4 was 18 years of age at the time of study entry and had a non-pyridoxine-responsive genotype. The patient received a KT on Study Day 739 (Month 26.4). The percent reduction from baseline in POx was 88.1% at Month 36. (**Figure 4**).[4]

Figure 4. Patient 4: POx, UOx:Cr, and Post-transplant eGFR through Month 36.[4]



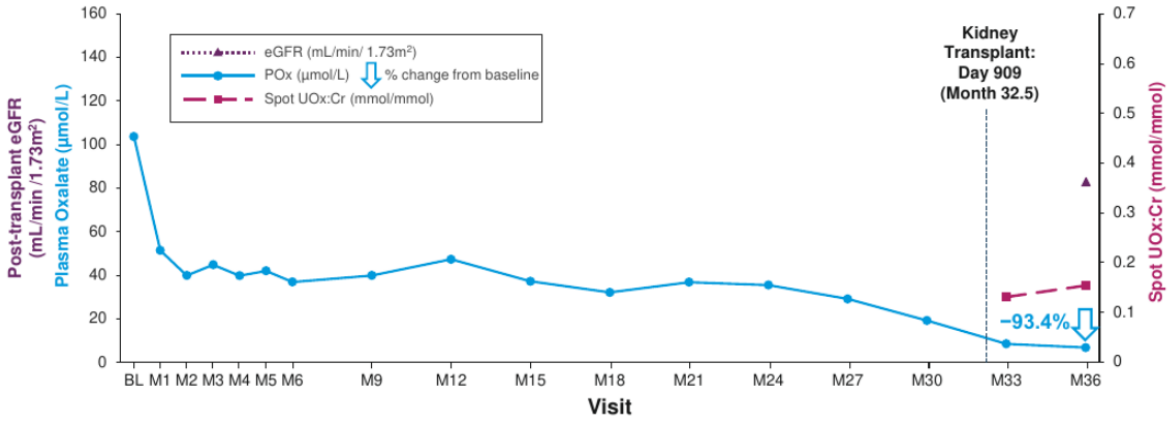
Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; POx = plasma oxalate; UOx:Cr = urinary oxalate:creatinine ratio.
From Somers et al.[4]

Patient 4 experienced moderate AEs of diarrhea and BK virus infection within the first month of KT. Both AEs were considered not related to lumasiran and were not resolved at the time of the data cut.[4]

Patient 5

Patient 5 was 1 years of age at the time of study entry and had a pyridoxine-responsive genotype. The patient received a KT at Study Day 909 (Month 32.5). The percent reduction from baseline in POx was 93.4% at Month 36. (**Figure 5**).[4]

Figure 5. Patient 5: POx, UOx:Cr, and Post-transplant eGFR through Month 36.[4]



Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; M = month; POx = plasma oxalate; UOx:Cr = urinary oxalate:creatinine ratio.
From Somers et al.[4]

Patient 5 experienced moderate AEs of *Clostridium difficile* infection and incision site discharge within the first month of KT, from which the patient recovered. The patient also experienced a mild AE of perinephric collection, which was not resolved. All 3 AEs were considered not related to lumasiran.[4]

As of Month 36, all 5 patients remained hemodialysis-free and continued treatment with lumasiran post-transplant. Overall, post-transplant AEs were frequent and included transplant-related complications that were not related to study drug. None of the patients experienced oxalate nephropathy post-transplant.[4]

CASE REPORTS

The following information provides an overview of published case reports regarding patients with PH1 who underwent isolated KT while receiving treatment with lumasiran. It is not intended to be an all-inclusive list or summary of relevant publications, abstracts, and manuscripts.

Choi M, et al. Recovery from severe heart failure in a patient with primary hyperoxaluria type 1 after treatment with lumasiran, pyridoxine, and kidney transplant. *AIMCC*. 2024;3(6). doi:10.7326/aimcc.2023.1428[5]

- A case report detailed the treatment outcomes of a 29-year-old male patient with PH1, severe cardiomyopathy, and heart failure who received an isolated KT in combination with lumasiran and pyridoxine therapy.
- The patient was diagnosed with kidney failure in August 2021 and received PD for 6 months. The patient developed severe heart failure (NYHA class III), with a LVEF of 25%, left ventricular septal hypertrophy (14 mm), and plasma NT-proBNP concentrations greater than 50,000 pg/mL. Endomyocardial biopsy specimens demonstrated interstitial inflammation with severe oxalate deposition.
- After 7 months of PD, the patient received parallel HD to optimize volume overload and lower POx. Initial POx level was 141.3 µmol/L in March 2022 and decreased to less than half after the patient received combined PD and HD with pyridoxine 160 mg daily.
- In mid-April, lumasiran 3 mg/kg was initiated, and POx was 29 µmol/L. Serial echocardiograms demonstrated an improvement in LVEF from 35% after initiation of HD to 43.8 ± 3.2% after the initiation of lumasiran therapy.
- In October 2022, the patient received a KT. Therapy with oral pyridoxine daily and subcutaneous lumasiran every 3 months was continued. There were no signs of rejection or oxalate deposition in allograft biopsy specimens collected 1 month post-transplant.
- At 6 months post-transplant, the patient's kidney function remained stable, with a creatinine of 1.8 mg/dL and eGFR of 49 mL/min/1.73 m^2. At 8 months post-transplant, POx was 9.5 µmol/L and cardiac function improved to NYHA class I, with an LVEF of 55% and NT-proBNP level of 309 pg/mL. A cardiac MRI conducted 8 months later demonstrated a reduction of the left ventricular mass index from 86 g/m^2 to 65 g/m^2 and normalization of T1 relaxation times.

Bacchetta J, et al. Lumasiran, isolated kidney transplantation, and continued vigilance. *N Engl J Med*. 2024;390(11):1052-1054. doi:10.1056/NEJMc2312941[6]

- Sellier-Leclerc et al. detailed the treatment outcomes of 5 patients with PH1 who underwent isolated KT and received lumasiran and proactive management during the immediate postoperative period. Patients were followed up for at least 6 months.[9]
- Bacchetta et al. reported data from at least 23 months of follow-up for each patient. All grafts continued to function at the time of the report, and no patients had nephrocalcinosis. In 4 of the patients, UOx:Cr was normalized or near normalized. Additional details regarding the treatment outcomes of individual patients are provided in the publication and supplement.[6,7]

Lombardi Y, et al. Stiripentol and lumasiran as a rescue therapy for oxalate nephropathy recurrence after kidney transplantation in an adult patient with primary hyperoxaluria type 1. *Am J Kidney Dis*. 2023;82(1):113-116. doi:10.1053/j.ajkd.2022.12.005[8]

- A case report detailed the treatment outcomes of an 51-year old adult patient with PH1 that was initiated on stiripentol and lumasiran treatment post-transplant.
- Prior to receiving the KT, the patient was started on pyridoxine at diagnosis (aged 49), but discontinued use after 1 month when symptoms compatible with peripheral neuropathy (mild paresthesias) appeared. Intensive chronic hemodialysis (5 sessions/week, 4 hours/session) was started at age 50.
- At 10 months following HD initiation, a living KT occurred. Pyridoxine 500 mg was restarted post transplantation and increased up to 1,750 mg per day without occurrence of adverse events. Stiripentol 1,250 mg twice daily was initiated at day 18 post-transplant and was increased to 2,250 mg twice daily at day 24. High UOx values persisted, and compassionate use lumasiran was granted and initiated at day 78 post-transplant. Serum oxalate concentration decreased from 27.8 µmol/L to 8 µmol/L, and UOx decreased from 2,890 µmol/d to 1,225 µmol/d.
- Systematic screening biopsies were performed at 3 months and 12 months post-transplant and showed a complete disappearance of previously existing oxalate crystals. At last follow-up on day 423, the patient was symptom free; serum creatinine was stable at 106 µmol/L with an eGFR of 69 mL/min/1.73m^2; and serum oxalate concentration was 20.2 µmol/L with a UOx:Cr ratio of 83 µmol/mmol.

Sellier-Leclerc A-L, et al. Isolated kidney transplantation under lumasiran therapy in primary hyperoxaluria type 1: a report of five cases. *Nephrol Dial Transplant*. 2023;38(2):517-521. doi:10.1093/ndt/gfac295[9]

- A retrospective report detailed 5 cases of patients with PH1 (median [range] age at transplantation: 26 [3-45]) that underwent isolated KT while on lumasiran therapy (median [range]: 13 [5-17] months of therapy before KT).
- Three of these patients received grafts from living donors, and all received intensive postoperative management which varied across treatment plans. Postoperative management across patients included (but was not limited to) hyperhydration, pyridoxine, dialysis, potassium citrate, immunosuppression with various agents, and lumasiran treatment. After a follow-up of at least 6 months, the 5 patients showed no indications of recurrent oxalate nephropathy nor signs of lactic acidosis with lumasiran treatment, with plasma oxalate levels ranging from not detected to 21 µmol. Two patients were followed up to 12 months. Additional details regarding the treatment outcomes of individual patients are provided in the publication.

Joher N, et al. Early post-transplant recurrence of oxalate nephropathy in a patient with primary hyperoxaluria type 1, despite pretransplant lumasiran therapy. *Kidney International*. 2022;101(1):185-186. doi:10.1016/j.kint.2021.10.022[10]

- A case report detailed the treatment outcomes of a 39-year-old female patient with PH1 who required a KT. After 3 years of conventional HD, the patient was initiated on daily HD in June 2020 and lumasiran was initiated in December 2020. In July 2021, serum oxalate concentrations normalized, allowing for a KT.
- The patient was treated post-transplant with high water intake, potassium citrate, vitamin B6, indapamide, and a low oxalate diet. On Day 25 post-transplant, the patient's kidney function declined, and kidney allograft biopsy showed Banff IIA acute rejection and oxalate nephropathy. The patient was treated for acute rejection, and preventive measures for the recurrence of oxalate nephropathy were maintained, including lumasiran on the seventh week post-transplant. There were no reports of adverse events or drug interactions.

Stone HK, et al Primary hyperoxaluria diagnosed after kidney transplant: A review of the literature and case report of aggressive renal replacement therapy and lumasiran to prevent allograft loss. *Am J Transplant*. 2021;21(12):4061-4067. doi:10.1111/ajt.16762[11]

- A case report detailed the treatment outcomes of a 7-year-old male pediatric patient diagnosed with PH1 following KT. Due to early post-transplant complications, PH1 was suspected and confirmed with genetic testing.
- Following the diagnosis of PH1, the patient received aggressive renal replacement therapy and lumasiran was initiated on day 34 post-transplant. The hemodialysis regimen was slowly weaned while following oxalate levels and discontinued at approximately 4 months post-transplant. In the first 5 months of lumasiran treatment, UOx decreased by 65.9%. UOx continued to decline since discontinuing hemodialysis, although levels remained above the upper limit of normal. The patient was also prescribed high fluid intake, pyridoxine, and potassium citrate.
- The patient was closely monitored for any AEs associated with treatment; overall, lumasiran was well tolerated.

OXLUMO PRESCRIBING INFORMATION – RELEVANT CONTENT

The USE IN SPECIFIC POPULATIONS provides the following information[13]:

Renal Impairment

No dose adjustment is necessary in patients with renal impairment including patients with kidney failure treated with hemodialysis. OXLUMO has not been studied in patients on peritoneal dialysis.

The CLINICAL PHARMACOLOGY section provides the following information[13]:

Pharmacokinetics

Table 3. Pharmacokinetic Parameters of Lumasiran

Excretion	
Primary Pathway	*Less than 26% of the administered dose of lumasiran is excreted unchanged into the urine within 24 hours with the rest excreted as inactive metabolite.*

ABBREVIATIONS

AE = adverse event; AKI = acute kidney injury, BL = baseline; eGFR = estimated glomerular filtration rate; HD = hemodialysis; KT = kidney transplant; LVEF = left ventricular ejection fraction; M = month; NA = not applicable; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; PH1 = primary hyperoxaluria type 1; PD = peritoneal dialysis; POx = plasma oxalate; UOx = urinary oxalate; UOx:Cr = urinary oxalate:creatinine ratio; UTI = urinary tract infection.

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