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Multicenter Long-Term Real World Data on Treatment With Lumasiran in Patients With Primary Hyperoxaluria Type 1

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Introduction: The RNA interference (RNAi) medication lumasiran reduces hepatic oxalate production in primary hyperoxaluria type 1 (PH1). Data outside clinical trials are scarce.

Methods: We report on retrospectively and observationally obtained data in 33 patients with PH1 (20 with preserved kidney function, 13 on dialysis) treated with lumasiran for a median of 18 months.

Results: Among those with preserved kidney function, mean urine oxalate (Uox) decreased from 1.88 (baseline) to 0.73 mmol/1.73 m^2 per 24h after 3 months, to 0.72 at 12 months, and to 0.65 at 18 months, but differed according to vitamin B6 (VB6) medication. The highest response was at month 4 (0.55, −70.8%). Plasma oxalate (Pox) remained stable over time. Glomerular filtration rate increased significantly by 10.5% at month 18. Nephrolithiasis continued active in 6 patients, nephrocalcinosis ameliorated or progressed in 1 patient each. At last follow-up, Uox remained above 1.5 upper limit of normal (>0.75 mmol/1.73 m^2 per 24h) in 6 patients. Urinary glycolate (Uglyc) and plasma glycolate (Pglyc) significantly increased in all, urine citrate decreased, and alkali medication needed adaptation. Among those on dialysis, mean Pox and Pglyc significantly decreased and increased, respectively after monthly dosing (Pox: 78–37.2, Pglyc: 216.4–337.4 μmol/l). At quarterly dosing, neither Pox nor Pglyc were significantly different from baseline levels. An acid state was buffered by an increased dialysis regimen. Systemic oxalosis remained unchanged.

Conclusion: Lumasiran treatment is safe and efficient. Dosage (interval) adjustment necessities need clarification. In dialysis, lack of Pox reduction may relate to dissolving systemic oxalate deposits. Pglyc increment may be a considerable acid load requiring careful consideration, which definitively needs further investigation.

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PH1 is an autosomal-recessive inherited disease of liver-specific glyoxylate metabolism, caused by loss of function of the peroxisomal enzyme alanine-glyoxylate aminotransferase. The absence or deficiency of alanine-glyoxylate aminotransferase results in overproduction of oxalate and glycolate, which are excreted via the urine.

Increased Uox causes calcium-oxalate kidney stones and/or nephrocalcinosis,[1] progressive chronic kidney disease and eventually kidney failure. The effects of

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excessive Uglyc might be harmless[2]; however, it is known from ethylene-glycol intoxication, that extremely elevated Pglyc can induce lactic acidosis.[3]

With deterioration of renal function, oxalate and glycolate are no longer adequately removed via the urine, and concentration of both metabolites in plasma rises. Elevated Pox induces calcium-oxalate supersaturation and thus, deposition of calcium-oxalate in most extrarenal tissue, (but not in liver),[4,5] a condition called systemic oxalosis. PH1, then, becomes a life threatening multisystemic disease. Pglyc values also increase accordingly in patients with PH1 with chronic kidney disease and kidney failure, though, they rarely reach the levels observed in ethylene glycol intoxication.[6,7]

Treatment of PH1 has been always a challenge.[8] Standard-of-care includes hyperhydration and alkaline citrate. Supraphysiological doses of VB6 medication given in patients with sensitive genotypes can achieve near or complete normalization of Uox and Uglyc.[9,10] In patients with kidney failure, Pox and Pglyc values were reducible accordingly.[11,12] It was also shown that isolated kidney transplantation in VB6-sensitive patients can result in comparable outcome to combined or sequential liver/kidney transplantation, which is the only curative treatment.[13]

Recently, a new *AGXT* genotype-independent RNAi medication, lumasiran (Oxlumo, Alnylam Pharmaceuticals, USA), was approved for treatment of PH1. Lumasiran targets the mRNA of glycolate oxidase (*HAO1* gene),[14] a key enzyme of substrate formation upstream the metabolic defect.

Pivotal clinical trials and its long-term follow-up reports clearly show significant reductions of Uox in patients with preserved kidney function or Pox values in patients on dialysis, an amelioration of clinical symptoms (less stones, regredient nephrocalcinosis), with an adequate safety profile.[15,16] However, glycolate values were only randomly reported. So far, 23 patients outside of clinical trials have been described, mostly from single-center experiences under variable conditions.[17-28] We report treatment with lumasiran in a large group of patients with PH1 with different renal functions from 12 European centers.

METHODS

We have retrospectively and observationally gathered data from 33 patients (patients [P]1–33, Table 1; Supplementary Table S1 and Supplementary Figure S1), who have received lumasiran since January 2021. Informed consents were signed for all (IRB votes: Bonn 113/14, CHUC_2021_02 and AEKNO 2021473). Fourteen patients were adults, 14 were females, and age range was from 2 days to 59 years old at starting treatment. Time of treatment ranged from 6 to 27 months (median 18 months). In the dialysis group ($n = 13$), 6 adults and 5 pediatric patients were on hemodialysis (HD), 1 adult patient received peritoneal dialysis (PD) and 1 child was treated with HD and PD. All nondialyzed patients had an estimated glomerular filtration above 45 ml/min at start of treatment, except for 1 (28 ml/min). They all had significant hyperoxaluria, and were either not treated with VB6, or did not have a profound Uox reduction as reason to be treated with lumasiran. In 2 late diagnosed (and VB6 naïve) adult patients with PH1, VB6 medication was added later (P8 and P9).

Lumasiran was provided in 4 monthly dosing (0, 1st, 2nd, and 3rd month), followed by quarterly 3 mg/kg body weight if >20 kg body weight. One patient (P23) received 4.5 mg/kg from the care taking physician. In infants and children <10 kg body weight (P17, P18, and P20) 6 mg/kg body weight was administered for the first 4 doses, followed by monthly dosing of 3 mg/kg body weight. Two patients (P31 and P32) had 1 vial of lumasiran available, so that the dosing was not always as recommended (Table 1). Four patients weighing 10–20 kg (P19, P26, P30, and P33), permanently received 6 mg/kg body weight, also when switched to quarterly dosing; in patients on HD, the dose was administered after dialysis. Because the experiences with the medication are scarce, we do present all patients' follow-up in individual tables/figures (Supplementary Table S1).

Data were analyzed for patients grouped either in preserved kidney function or HD, only considering those with the same dose regimen, and according to VB6 medication. Only time points with $n \geq 3$ were considered for analysis. Response was defined according to the Alnylam's study definitions as follows: normalization (Uox < 0.5 mmol/1.73 m^2 per day), near normalization (0.5 < Uox < 0.75 mmol/1.73 m^2 per day, as 1.5 upper limit of normal),[15] or partial response (Uox > 0.75 mmol/1.73 m^2 per day but below baseline), at months 3, 12, and 18 after start of treatment. In patients with kidney failure, Pox decline as compared to baseline was considered; however, no cutoff was used. Infants and children with age-specific dosing regimen, the adult patient on PD, and data of P23, who received an increased dosage regimen, are presented singularly.

Next to standard blood drawings for kidney function, white blood cell count differentiated, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, gammy glutamyl transferase, bilirubin, creatine kinase M and B subunit, N-terminal pro-B-type natriuretic peptide, parathyroid hormone, alkaline phosphatase and vitamin D, serum B6, blood pH, HCO_3^-, base excess and serum lactate were measured.

Table 1. Primary hyperoxaluria patients in Europe treated with RNAi medications outside clinical trials

Patient n° and gender	Age of diagnosis (Genotype)	Clinical situation before RNAi	Age of starting RNAi medication and dose	Serum creatinine in mg/dl eGFR/mGFR in ml/min × 1.73 m^2	Duration of RNAi and concomitant medication	Outcome/ Side effects	Other relevant information at last dosing
Preserved kidney function group							
1 Male	7 years old (c.327delG/ c.327delG)	External ear malformation, psoriasis. Stones and grade II–III nephrocalcinosis; but no stone removal procedures. Normal speckle echocardiography (GLS of −23.8%), and bone MRI. No systemic oxalosis.	17 yrs 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: SCr: 0.9 eGFR: 112 Follow up: M12 Scr: 1.0 eGFR: 96 M24 SCr: 0.9 eGFR: 104	24 mos + hyperhydration + citrate + VB6 (7.6 mg/kg) Sodium-potassium dosage was doubled because of Ucit of 0.43 mmol/1.73 m^2/d	Nephrocalcinosis remained grade II–III. Stone development in right kidney, needing stone removal procedure. Bone MRI normal. Mal compliance to check-ups, and concomitant medication.	Deterioration of psoriasis especially at sculp. Serum lactate 1.2 mmol/l Anion gap: 14.3 mmol/l.
2 Female	3 years old (c.254C>A/ c.994_995delTG)	Stone removal procedures: 2 × PNL right kidney, ESWL right once. 5 stones left, 1 stone in right kidney. Unresponsive to VB6 Normal speckle echocardiography and bone MRI. No systemic oxalosis	9 yrs 3mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr: 0.9 eGFR 64.7 Follow up: M12 Scr: 1 eGFR: 60.7 M24 Scr: 1 eGFR: 63.6	24 mos + hyperhydration + citrate sodium-citrate/potassium hydrogen carbonate dosage increase (dose doubling) at Ucit of 1.97 mmol/1.73 m^2, later switch to slow release potassium bicarbonate/ potassium citrate with increased dosage post 8th Lumasiran dosage	Stones *in situ*, but no new development. Injection site pain and fainted at the first 2 dosages. Speckle echocardiography remained normal (GLS −23.8%).	Developed a non-calcium oxalate calcification at the right cheek. Increased dose to 4.5 mg/kg of lumasiran after M24. Serum lactate: 2.63 mmol/l Anion gap: 10.5 mmol/l
3 Male	17 years old (c.121G>A/ c.846+1G>A)	Hashimoto thyroiditis. Multiple stones in left kidney, medullary nephrocalcinosis. No stones in right kidney. ESWL left and URS right kidney. Normal speckle echocardiography (GLS −23 %). No systemic oxalosis.	30 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr 1.1 eGFR: 105 Follow up: M12 Scr 0.9 eGFR 118 M21 Scr 1.0 eGFR: 107	21 mos + hyperhydration + VB6 (5 mg/kg) + L-thyroxin + Allopurinol + sodium hydrogen carbonate dose was increased from 3 x 3 to 3 x 4 g per day at Ucit of 1.49 mmol/ 1.73 m^2/d	No new stones, stones in left kidney Speckle echocardiography: GLS -16.3 % Normal bone MRI and eye exam.	Switched promptly from Nedosiran to Lumasiran Pain in big toes, attributed to arthrosis, resolved with insoles. Allopurinol was stopped Serum lactate: 1.58 mmol/l ALT: 67U/l
4 Male	2 years old (c.33dupC /c.525-1G>A)	Pyonephrosis with obstructive bilateral kidney stones. Bilateral nephrostomy. PCNL and URS right, and PCNL left kidney. Unresponsive to VB6. No systemic oxalosis.	6 years old 3 mg/kg monthly (the first 4 doses), then quarterly	*Prior:* Scr: 0.8 eGFR: 59.4 *Follow up* M12 Scr: 0.8 eGFR: 74 M18 Scr: 0.7 eGFR: 74.9	18 months + hyperhydration + citrate Modified Shol solution switched to sodium citrate/potassium hydrogen carbonate, dosage remained unchanged of 12.6 mmol/d citric acid	One new stone in the left and right kidney each. Severe psychological problems because of pain at injection side, needed psychological help.	After 8th dose, lumasiran was stopped because of psychosocial side effects. Serum lactate: 1.92 mmol/l
5 Female	12 yrs old (c.508G>A/ c.846-3C>G)	Multiple stones. ESWL, post stone street in ureter. No systemic oxalosis.	25 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr: 1.1 eGFR: 80 Follow up: M12 Scr: 1.2	21 mos + hyperhydration + VB6 (9.4 mg/kg) + valsartan + Na-hydrogen carbonate Switched to potassium citrate/	Better serum B6 levels, significant hypocitraturia. Dizziness. Skin irritation after each dose. No stones *in situ* before and	Tachycardia, not related to antihypertensive medication. Lumasiran was stopped at M21 Serum lactate: 2.28 mmol/l Anion gap: 11.3 mmol/l AST: 49 U/l

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Patient n° and gender	Age of diagnosis (Genotype)	Clinical situation before RNAi	Age of starting RNAi medication and dose	Serum creatinine in mg/dl eGFR/mGFR in ml/min × 1.73 m^2	Duration of RNAi and concomitant medication	Outcome/ Side effects	Other relevant information at last dosing
				eGFR: 75 M18 Scr: 0.8 eGFR: 81	potassium bicarbonate at Ucit of 0.83 mmol/1.73 m^2/d only after M21 + amlodipine (stopped at M15)	under treatment, but 3-4 twinkling signs in left kidney.	ALT: 43 U/l LDH: 269 U/l
6 Male	3 months old 4 years old (genetic) (c.1078C>T/ c.1078C>T and c.584T>G)	Myopia with astigmatism. Multiple bilateral stones and stone passages. Unresponsive to VB6. No systemic oxalosis.	10 years old 3 mg/kg monthly (the first 4 doses), then quarterly	*Prior:* Scr: 0.6 eGFR: 98 *Follow up:* M12 Scr: 0.6 eGFR: 101.9 M18 Scr: 0.5 eGFR: 124.8	18 months + hyperhydration + citrate Switched from modified Shol solution to potassium citrate/ potassium bicarbonate at Ucit of 0.81 mmol/1.73 m^2/d, M9	Huge stone burden with increasing sizes, especially on the right side. Stone removal procedure (x2 PCNL + ESWL in right kidney, x1 PCNL and URS in left kidney) at M10-12. Thereafter, developed 3 stones left, 2 stones right kidney.	Lumasiran dose increased to 4.5 mg/kg after M18 Serum lactate: 1.05 mmol/l Anion gap: 0.2 mmol/l
7 Male	9 yrs old (c.107G>A / c.731T>A)	Stones and stone removal procedures. Hydronephrosis left kidney.	13 yrs old 3mg/kg monthly (the first 4 doses), then once every 3 months	Prior: Scr: 1.1 eGFR: 53.1 Follow up: M12 Scr: 1.3 eGFR: 54 M18 Scr: 1.1 eGFR: 65.7	18 mos + hyperhydration + citrate + VB6 (5 mg/kg) sodium citrate, dosage remained stable	Hyperechoic right kidney, but no stones.	Lumasiran dose increased to 4.5 mg/kg after M15 Serum lactate 1.28 mmol/l Anion gap: 7.0 mmol/l.
8 Male	56 yrs old (c.33delC/ c.508G>A)	Kidney stones Several URS. Urosepsis followed by acute kidney injury. No systemic oxalosis. No standard medication at start lumasiran.	56 yrs old 3mg/kg monthly (the first 4 doses), then quarterly	Prior Scr: 1.4 eGFR: 55.8 Follow up: M12 Scr: 1.28 eGFR: 61.3 M27 Scr: 1.3 eGFR: 58.1	27 mos + hyperhydration + citrate + VB6 (started at M12, 3 mg/kg) potassium hydrogen carbonate, dosage remained stable	No clinical sequelae	Sibling died 40 years ago from systemic oxalosis in his early twenties on dialysis.
9 Female	59 yrs old (c.33delC/ c.508G>A)	2 stones, first manifestation in late adulthood. No systemic oxalosis. No standard medication at start lumasiran.	59 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior Scr: 0.9 eGFR: 69 Follow up: M12 Scr: 0.84 eGFR: 75.3 M24 Scr: 0.84 eGFR: 75.3	24 mths + hyperhydration + citrate + VB6 (started at M12, 2 mg/kg) potassium hydrogen carbonate, no increase in dosage although Ucit 0.83 mmol/1.73 m^2/d at M18	No clinical sequelae	Sibling died from systemic oxalosis in his early twenties on dialysis
10 Female	6 yrs old (c.107G>A/ c.107G>A)	Multiple stones in both kidneys, and ureter. PCNL in right kidney. No systemic oxalosis.	7 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr 1.1 eGFR 51.4 Follow up:	18 mos + hyperhydration + citrate + VB6	No clinical sequelae VB6 stopped at M9	Serum lactate: 1.7 mmol/l

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				M12 Scr 0.9 mg/dl eGFR 67 M18 Scr 0.8 mg/dl eGFR: 78.5	75 mEq (8.1 g) potassium citrate, 15 mEq (1128 g), magnesium citrate		
11 Female	3 yrs old (c.508G>A/ c.823A>C)	Nephrocalcinosis No systemic oxalosis	5 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr 0.7 eGFR 59.6 Follow up: M12 Scr 0.6 eGFR 77.1 M15 Scr 0.6 eGFR 77.1	15 mos + hyperhydration + citrate + VB6 (14.3 mg/kg) Increase in potassium citrate medication, later change to sodium bicarbonate 2meq/kg body weight/d	Urine citrate excretion zero at 6th dose. Recurrent abdominal pain post M15.	At M9 Serum lactate: 3.0 mmol/l At M12 Serum lactate: 1.6 mmol/L
12 Female	32 yrs old (c.731C>T/ c.33dupC)	Bilateral lithiasis since infancy. Recurrent hematuria, UTI, pyelonephritis and pyelolithotomy. Right kidney atrophic. Multiple (ESWL and URS), and spontaneous stone passages. No systemic oxalosis. Proteinuria: 1-1.5 gr/day.	34 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: SCr: 2.35 eGFR 27 (28.37 by Iohexol) Follow up: M12 Scr 1.88 eGFR: 35 (30.12 by Iohexol) M21 SCr 2.08 mg/dl; eGFR 29 ml/min	24 mos. + hyperhydration + potassium citrate prolonged release (bad tolerance always) + VB6 (8 mg/kg/day) + magnesium + bicarbonate + losartan	Injection site reaction, more prominent during first 3 doses. Since 5th dose, multiple events of dysuria without fever, or UTI; stone passage requiring double-J. After 7th dose, refers transient amaurosis fugax (ophthalmologic exploration normal).	Chronic hypocitraturia before lumasiran, with metabolic acidosis during the whole treatment, corrected with bicarbonate.
13 Male	4 yrs old (c.731C>T / c.731C>T)	Adenoidectomy and acute suppurative otitis. Bilateral medullar nephrocalcinosis. Albuminuria.	5 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr: 0.85 eGFR: 62 Follow up: M12 Scr: 0.82 eGFR: 64 M24 Scr: 0.91 eGFR: 60	24 mos + hyperhydration + potassium citrate prolonged release + VB6 (13mg/kg/day) + magnesium + enalapril	Headache and transient erythema after first doses. After 5th and 10th doses, no stones and no nephrocalcinosis. Recurrent unspecific abdominal pain.	Eye and heart without signs of oxalosis. Progressive rise in albuminuria, pharmacologically treated, showing urticaria that resolved after few weeks.
14 Male	39 yrs old (c.731C>T/ c.731C>T)	Lithotomy during infancy, staghorn calculus. Multiple ESWL, PCNL (x2), and URS. Hypertension with good control. Dyslipidemia, hyperuricemia. No systemic oxalosis.	49 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr: 1.52 eGFR: 56 (57.35 by iohexol) Follow up: M12 Scr 1.54 mg/dl eGFR: 55 (47.02 by iohexol)	14 mos + hyperhydration + potassium citrate prolonged release + VB6 (8 mg/kg/d) + allopurinol + statins + olmesartan	Spontaneous stone passage after 2nd and 3rd dose. Dizziness and continuous abdominal pain irradiated to left testis after 5th dose. Required ESWL (x2) after 6th dose.	Lumasiran stopped after 7th dose, expected Uox values not reached and clinical situation remained equal Two asymptomatic PH1 sisters.

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Table 1. (Continued) Primary hyperoxaluria patients in Europe treated with RNAi medications outside clinical trials

Patient n° and gender	Age of diagnosis (Genotype)	Clinical situation before RNAi	Age of starting RNAi medication and dose	Serum creatinine in mg/dl eGFR/mGFR in ml/min × 1.73 m^2	Duration of RNAi and concomitant medication	Outcome/ Side effects	Other relevant information at last dosing
15 Female	3 yrs old (c.731C>T / c.731C>T) Family screening.	Bilateral nephrocalcinosis, multiple spontaneous stone passages. Hypocitraturia. Albuminuria. Vitamin D deficiency. Iron deficiency without anemia.	6 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr: 0.50 eGFR 97 (99.7 by iohexol) Follow up: M9 Scr: 0.53 eGFR 99	10 mos + hyperhydration + potassium citrate prolonged release + VB6 (20 mg/kg) + enalapril	After 5th dose: bilateral lithiasis, without nephrocalcinosis. Otherwise, asymptomatic.	Eye and heart without signs of oxalosis.
16 Male	12 yrs old (c.33dupC/ c.33dupC)	Multiple bilateral kidney stones. URS both sides. Unresponsive to VB6 No systemic oxalosis	13 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr: 0.81 eGFR 83 Follow up: M9 Scr: 0.74 eGFR: 93	12 mos + hyperhydration + citrate sodium-potassium citrate 1137 mg of citric acid 3 times per day.	Stone removal at M3	Serum lactate: 2.04 mmol/l AST: 41 U/l
17 Male	3 mos old (c.33dupC/ c.33dupC)	Nephrocalcinosis. Neonatal acute kidney injury. Gitelman syndrome, preterm infant. Lactic acidosis at diagnosis, lactate of 8.11 mmol/l. No systemic oxalosis. Unresponsive to VB6.	3 mos old 6 mg/kg monthly the first 3 months, then 3 mg/kg monthly. From 10th dose again 6 mg/kg monthly	Prior: Scr: 0.49 Follow up: M12 Scr: 0.37	16 mos + hyperhydration (via gastric tube) + citrate Modified Shol solution, dosage remained stable	Progressive nephrocalcinosis (grade IIc).	Normal psychomotor development, normal growth. Serum lactate: 4.2 mmol/l
18 Male	3 mos old (c.33dupC/ c.33dupC)	Kidney stones. Neonatal acute kidney injury. Lactic acidosis at diagnosis, serum lactate of 3.07 mmol/l. No systemic oxalosis. Unresponsive to VB6.	3 mos 6 mg/kg monthly the first 3 months, then 3 mg/kg monthly. From 10th dose again 6 mg/kg monthly	Prior: SCr: 0.51 Follow up: M12 Scr: 0.27	16 mos + hyperhydration (via gastric tube) + citrate Modified Shol solution, dosage remained stable	Stable nephrocalcinosis (grade III).	Normal psychomotor development, normal growth. Serum lactate: 3.19 mmol/l
19 Female	11 mos old (c.731C>T / c.731C>T) Family screening.	2-3 stones in right kidney. Bone density augmented in knee, and both hands. Vitamin D deficiency. Secondary hyperparathyroidism. Iron deficiency without anemia, left ventricular hypertrophy.	1.8 yrs old 6 mg/kg monthly (the first 4 doses), then quarterly	Prior: Scr: 0.30 eGFR 120 Follow up: M9 Scr: 0.4 eGFR 94.5	11 mos + hyperhydration + potassium citrate prolonged release + VB6 (15 mg/kg) + vitamin D supplementation + iron + enalapril	After 5th dose: no stones. Otherwise, asymptomatic.	Eye and heart without signs of oxalosis.
20 Male	Prenatal diagnosis (c.731T>C/ c.731T>C)	Asymptomatic. No stones. Normal speckle echocardiography.	2 ds old 6 mg/kg monthly	Prior: Scr: 0.8 Follow up: M4 Scr: 0.17	6 mos + citrate + VB6 (5 mg/kg) dosage increase post 1st dosage from 3 × 540 mg potassium citrate to 2 × 1080 plus 1 × 540 mg	Normal speckle echocardiography. Ultrasound at M2 with possible nephrocalcinosis No acidosis	Serum lactate: 1.4 mmol/l
Dialysis group							
21 Male	20 yrs old (c.33dupC / c.508G>A)	Multiple stones. Multiple ESWL, PCNL (1x), URS left side. Double-J insertion without clinical	33 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Kidney failure-HD 6 × 3 h HD weekly	24 mos + VB6 (10 mg/kg) + antihypertensive medication	No changes in bone MRI, neither in speckle (GLS-14 %). Severe systemic oxalosis. Left heminephrectomy because	M24: Calcium 2.0 mmol/l, Protein: 5.2 mg/dl, GOT 41 U/l,

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		evaluation for 3 years. One double-J removed, other encrusted in place. Nephrectomy right. Systemic oxalosis in bone (by bone MRI and biopsy) and heart by speckle echocardiography (GLS -17 %)				of recurrent infections. Empyema in the left knee. Shunt thrombosis Increase in dosage of lumasiran to 4.5 mg/kg planned + oral stiripentol	GGT 96 U/l, AP 571 U/l, LDH 651 U/l, PTH 409 pg/ml, NT-proBNP 18000 Serum lactate: 2.4 mmol/l Anion gap: 13.1 mmol/l
22 Male	51 yrs old (c.508G>A/ c.508G>A)	Multiple ESWL and URS. Systemic oxalosis in bone and heart. Renal anemia, hyperparathyroidism, chronic heart insufficiency, arterial hypertension, hyperlipidemia.	52 yrs old 3 mg/kg monthly (the first 4 doses), then quarterly	Kidney failure- HD Home hemodialysis every other day × 4 h	21 mos + VB6 (5.4 mg/kg) + sodium hydrogen carbonate 3g/d on nondialysis days + antihypertensive medication	No changes neither in bone MRI, nor in speckle echocardiography.	Lumasiran was stopped after M20 because of no change in Pox and Pglyc. Serum lactate: 0.9 mmol/l Pox after stop of lumasiran: 26 µmol/l PTH 280 pg/ml, NT-proBNP 24265 ng/l
23 Female	49 yrs old (c.322T>C / c.322T>C)	3 open stone removal surgeries right and 2 left kidney. No VB6 given Severe systemic oxalosis of bone and heart.	52 yrs old 4.5 mg/kg monthly (the first 4 doses), then quarterly	Kidney failure - HD HD 3- 4 times per week only (because of clinical situation)	24 mos + VB6 (at M15) (10 mg/kg) + sodium hydrogen carbonate 2 g on non HD days + HD-related medication + erythropoietin + ferrum + vitamin D	Metabolic acidosis, treated with bicarbonate. VB6 withdrawal. Unable to walk due to bone pain and severe scoliosis. Removed from LKTx list, currently not transplantable. M20: Bone MRI amelioration. Died at M24 due to bacterial infection and COVID-19.	Head with sclerotic bone lesions. 25(OH)D3 4.7 ng/ml, GOT 117 U/l. GGT 214 U/l, AP 506 U/l, LDH 793 U/l, CK 397 U/l (< 170), CK-MB 685 U/l, CK-BB 317 U/l, NT-proBNP 4679 Serum lactate: 6.93 mmol/l
24 Female	45 yrs (c.508G>A /c.508G>A)	Post hysterectomy, post cholecystectomy, secondary hyperparathyroidism, renal anemia, arterial hypertension, hypothyroidism, glaucoma. No stones. No systemic oxalosis.	50 yrs old 3mg/kg monthly (the first 4 doses), then quarterly	Kidney failure - HD Hemodialysis 3 × 5 h per week	22 mos + VB6 (5.4 mg/kg) + sodium hydrogen carbonate 3 g/d on non dialysis days + HD-related medication + mycophenolate (after iKTx) + tacrolimus (after iKTx) + prednisone (after iKTx)	iKTx after 8th dose. Acute kidney injury post surgery, related to arterial stenosis. After stenting, amelioration of kidney function. Lumasiran stopped at M22	Stopped mycophenolate before 10th dose due to severe diarrhea, prednisone increased BUN 42 mg/dl, AST 36 U/l, GGT 176 U/L, LDH 297 U/l, NT-proBNP 1920 ng/l Serum lactate:1.32 mmol/l
25 Female	57 yrs old (c.508G>A/ c.994_995del)	Renal anemia, secondary hyperparathyroidism, hypocalcemia, hyperphosphatemia, metabolic acidosis. Pushback proximal ureteral stone left kidney treated with URS. No systemic oxalosis in heart (GLS −18%).	59 yrs old 3 mg/kg monthly (the first 4 doses), then once every 3 months	Kidney failure - HD HD 3 × 4 h per week since M2 (still diuresis of > 1.5 L)	15 mos + VB6 (10.7 mg/kg) + sodium hydrogen carbonate 2 g on non HD days + HD-related medication	Stable clinical condition. Metabolic acidosis, thus bicarbonate dosage increased. Little bilateral kidneys, 6 stones each. Bone and eyes without oxalosis. Speckle echocardiography with GLS −16.5 %	PTH 526.9 pg/ml NT-proBNP 1982 ng/l Serum lactate:1.4 mmol/l Anion gap: 18.9 mmol/l
26 Female	4 mos old (c.584T>G / c.584T>G)	Renal failure, nephrocalcinosis. No stones. Unresponsive to VB6 Systemic oxalosis in bone marrow,	2.4 yrs old Lumasiran 6mg/kg monthly started in overlap with Nedosiran for first 3	Kidney failure - HD Combined HD and PD 5-6 times weekly HD	15 mos + HD-related medication + growth hormone + nedosiran (3 first doses)	At M9: Retinal oxalate deposition without reduced vision. Oxalate osteopathy.	No acidosis on intensified dialysis (no bicarbonate required).

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Table 1. (Continued) Primary hyperoxaluria patients in Europe treated with RNAi medications outside clinical trials

Patient n° and gender	Age of diagnosis (Genotype)	Clinical situation before RNAi	Age of starting RNAi medication and dose	Serum creatinine in mg/dl eGFR/mGFR in ml/min × 1.73 m^2	Duration of RNAi and concomitant medication	Outcome/ Side effects	Other relevant information at last dosing
		repeated red blood cell infusions. Bilateral distal fracture of radius bones before Lumasiran Nedosiran 2 mg/kg/monthly started at 15 weeks old	dosages. Then, Lumasiran 6 mg/kg quarterly in the 5th and 6th dose, and changed to 6 mg/kg bimonthly	plus daily PD overnight.		New catheter required at 2.5 years old.	
27 Male	12 yrs old (c.731C>T / c.731C>T)	Spontaneous stone passage. Atrophic and calcified left kidney, and echogenic right kidney. Epilepsy, anemia and hypertension, secondary hyperparathyroidism. Hypertrophic left ventricle (ejection fraction 39%). Fibrotic myocardium by biopsy without deposits. Sclerosis in distal ulnar bone. No oxalosis in eyes.	19 yrs old 3 mg/kg monthly during first 4 doses, then quarterly	Kidney failure - HD Started HD (4h × 6 days a week) at CKD4	15 mos + VB6 (10 mg/kg/d) + valproic acid + HD-related medication + antihypertensive medication	After 6th dose: severe calcification of right kidney with multiple lithiasis. Laparoscopic nephrectomy of right kidney. Amelioration of heart ejection fraction (58.6%).	Pending parathyroidectomy. Convulsive event before 8th dose (related to bad adherence to valproic acid). PTH: 722 pg/ml (normal 12–65).
28 Male	12 yrs old (c.731C>T / c.731C>T)	Multiple bilateral lithiasis, nephrocalcinosis, metabolic acidosis, hyperuricemia. Nephrostomy, ESWL and double J. Left renal atrophy, recurrent UTI, arterial hypertension, albuminuria. Echocardiography showed type 1 second grade atrioventricular blockage.	16 yrs old 3 mg/kg monthly during first 4 doses, then quarterly	Kidney failure - HD Started HD (4h × 6 days a week) at CKD4	8 mos + VB6 (10 mg/kg) + potassium citrate prolonged release + bicarbonate + HD-related medication + antihypertensive medication	After 4th dose: laparoscopic nephrectomy of left kidney. After 5th dose: laparoscopic nephrectomy of right kidney.	Received combined LKTx after 5th dose Scr 1.21 mg/dl 3 months post LKTx. Stable clinical outcome after Tx.
29 Female	56 yrs old (c.731C>T / c.731C>T)	Lithotripsy. Recurrent deep vein thrombosis, arterial hypertension, hypothyroidism, anemia requiring high doses of erythropoietin. Atrial fibrillation, heart ejection fraction 38%. iKTx at 56 years old, lost due to oxalate nephropathy, then diagnosed. Myocardium and bone biopsy with oxalate deposits. Systemic oxalosis in heart, bone, eyes.	57 yrs old 3 mg/kg monthly during first 4 doses, then quarterly	Kidney failure - PD started HD, but switched to PD because of HD vascular access problems	21 mos + VB6 + erythropoietin + anticoagulant	Reduce erythropoietin needed. Recovered weight. Ameliorated ejection fraction (68%) No alteration of Ca-P ratio. No elevation of liver enzymes.	Extramedullary hematopoiesis in native kidney.[29]
30 Male	22 mos old (c.919delC/ c.919delC)	Psychomotor retardation and growth failure. Bilateral nephrocalcinosis. CKD in early infancy. PD, then switched to HD. Unresponsive to VB6 Bone osteopenia and systemic oxalosis. Irregular vertebral morphology at D8-L3. Eyes: bilateral macular lesion with oxalate deposition.	2.5 yrs old 6 mg/kg monthly during first 4 doses, then quarterly	Kidney failure - HD (3h + 6 d/wk)	9 mos + HD + erythropoietin + gastrotomy button due to anorexia + growth hormone	Gained weight after 6 months of treatment. Ameliorated psychomotor development. Bone and eyes: same lesions.	No clinical sequelae.

(Continued on following page)

Table 1. (Continued) Primary hyperoxaluria patients in Europe treated with RNAi medications outside clinical trials

Patient n° and gender	Age of diagnosis (Genotype)	Clinical situation before RNAi	Age of starting RNAi medication and dose	Serum creatinine in mg/dl eGFR/mGFR in ml/min × 1.73 m^2	Duration of RNAi and concomitant medication	Outcome/ Side effects	Other relevant information at last dosing
31 Male	5 mos old (c.653C>T / c.653C>T)	Already in renal failure at first admission (3 months). PD at diagnosis then switched to HD 3 months later. Unresponsive to VB6. Systemic oxalosis in eyes and bones.	17 mos old 5.2 mg/kg-4.3 mg/kg/mo (dose reduction with weight gain, shared one vial with patient 32)	Kidney failure - HD 5–6 days × 3 h	15 mos + HD-related medication + gastrotomy button + VB6 (18.5 mg/kg)	Worsening retinal oxalate deposits.	Prepared for liver-kidney transplantation Serum lactate: 1.6 mmol/l
32 Female	3 mos old (c.454T>A/ c.533G>A)	PD at diagnosis. HD started at age 9 months. Oxalosis: retinal oxalate depositions.	15 mos old 6 mg/kg/mo-4.7 mg/kg/mo (dose reduction with weight gain, shared one vial with patient 31)	Kidney failure - HD HD 5–6 times 3 h per week	15 mos + VB6 + HD-related medication + gastrotomy button + VB6 (16.33 mg/kg)	Liver enzymes normal. No acidosis. Worsening retinal oxalate deposits.	Prepared for liver-kidney transplantation. Serum lactate: 1.3 mmol/l
33 Male	6 mos old (c.731T>C/ c.731T>C)	Renal failure. PD since diagnosis, additional HD started at age 22 months. Anemia, temporary pancytopenia, secondary hyperparathyroidism, metabolic acidosis, failure to thrive. Systemic oxalosis in eyes and heart, and bone (repetitive pathological fractures) Nedosiran 2 mg/kg monthly for 2 years, stopped one month before lumasiran.	4.3 yrs old 6 mg/kg monthly during first 4 doses, then quarterly.	Kidney failure - HD HD 5 times 2.5–3 h weekly	18 mos + VB6 + HD-related medication	Liver enzymes: normal. No acidosis (prevented by intensified dialysis). Repetitive bone pathological fractures.	Prepared for liver-kidney transplantation.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; CK, creatine kinase; eGFR, estimated glomerular filtration rate (Schwartz 2009 formula for patients <18 years, CKD-EPI for patients >18 years old); mGFR, measured glomerular filtration rate with iohexol; ESWL, extracorporeal shock wave lithotripsy; GGT, gammy glutamyl transferase; GLS, global longitudinal strain in speckle echocardiography, normal < −18%; HD, hemodialysis; iKTx, isolated kidney transplantation; LDH, lactate dehydrogenase; LKTx, combined liver/kidney transplantation; MRI, magnetic resonance imaging; NT-proBNP, B-type natriuretic peptide; P, phosphate; PD, peritoneal dialysis; PNL, percutaneous nephrolithotomy; Pox, plasma oxalate; PTH, parathyroid hormone; RNAi, RNA interference; Screa, serum creatinine; Tx, transplantation; URS, ureterenoscopy; UTI, urinary tract infection.
Normal values of biochemical parameters: anion gap <11 mmol/l, serum lactate <2.2 mmol/l.
Modified Shol solution = 250 mmol/l potassium citrate (81.67 mg/l citric acid); sodium citrate, potassium hydrogen carbonate 1197 mg citric acid per effervescent; potassium citrate and potassium carbonate slow release 847 mg citric acid per 24 meq package, and potassium citrate prolonged released 1080 mg citric acid.
For urine values see figures and supplementary tables. Follow-up procedures regarding imaging were different between countries. Gender is subdivided into male and female.

Anion gap was calculated when possible. Pathological values are shown in Table 1. Pox and Pglyc were determined before the first and all further lumasiran dosages, when applicable.

Urine collections in patients with preserved kidney function were done equally, at baseline, before every dosage, and during intervals of quarterly dosing. With the exception of infant data, 24-hour urine results are presented. Excretion parameters are related to body surface area of 1.73 m^2/d.[30] Collection completeness was checked with creatinine evaluation. Other lithogenic and inhibitory parameters were also analyzed; however, next to oxalate and glycolate, we only refer to urinary citrate (Ucit) analysis, which was possibly influenced by medication.

Pox, Pglyc, and plasma citrate (Pcit) were measured following a well-known optimized protocol (normal values <7.4, <10.3 and <320 μmol/l, respectively).[31,32] Urines were collected without preservation; however, promptly after collection, the aliquot for Uox, Uglyc, and Ucit determination was acidified to a urine pH of 1.5 to 3. All samples were analyzed by ion chromatography/mass spectrometry.[31,32] Urinary and serum creatinine were quantified by Jaffe reaction (calibrated with traceable isotope dilution mass spectrometry) and measured by ultraviolet-visible spectrophotometry. All parameters were analyzed in the Wisplinghoff laboratory (Cologne, Germany).

All patients with preserved kidney function received standard-of-care treatment consisting of hyperhydration, citrate medication and eventually VB6. All patients on dialysis received standard kidney failure medications, for alkalinization sodium bicarbonate was provided. HD regimens were kept as prescribed at baseline. This, of course, includes tiny changes based on catheter-related or fistula-related problems, or an unplanned missed dialysis based on other events (e.g., surgery). However, sessions per week, filter, blood, and dialysate flow were kept stable (Table 1). All patients, with the exception of 1, had center-based HD, 1 patient (P22) dialyzed at home (Table 1). Patient 29 had PD only because of fistula-related problems and the wish to remain with PD.

When possible, systemic oxalate depositions were checked in the patients on HD by bone magnetic resonance imaging (MRI) of left knee,[33] speckle tracking echocardiography,[34] retinal examinations,[35] or bone and myocardial biopsies.

Descriptive statistics (mean ± SD) of group analysis, nonparametric paired Wilcoxon test, nonparametric Spearman correlation analysis, and graphs were performed with GraphPad Prism v9.5.1 (Boston, MA). All data were additionally placed in a primary hyperoxaluria registry (www.ph-registry.net).

RESULTS

Preserved Kidney Function

Median follow up of the 20 patients with preserved kidney function was 18 months. Individual follow-up is shown in Supplementary Table S1. In those treated with 3 mg/kg monthly for the first 4 months and then quarterly (P1–P16), mean Uox declined from 1.88 (SD 0.8, $n = 16$) to 0.73 mmol/1.73 m^2 per day (0.26; mean reduction −61.3 %, $n = 16$) after monthly dosing (month [M]3), to 0.72 (0.3; −61.8%, $n = 15$) at M12, and 0.65 mmol/1.73 m^2 per day (0.2; −65.7 %, $n = 12$) at M18 (Table 2). The highest reduction of Uox (0.55, SD 0.26) was achieved 1 month after the 4th dose (−70.8%, $n = 9$). Normal Uox was achieved in 4 patients at M3, 4 at M12, and 5 at M18. Near normal values were achieved in 6 at M3, 5 at M12, and 3 patients at M18; and partial Uox response in 6 at M3, 6 at M12, and 4 patients at M18. At patients' last follow up, Uox was normal in 3, near normal in 7, and in 6 it was >1.5 upper limit of normal.

Comparing patients with VB6 to those without, mean Uox over time was lower in the VB6 patients, but percent reduction of Uox over time was higher in the non-VB6 group (Table 2, Figure 1a and b).

Mean Uglyc significantly increased from 2.13 (SD 2.3, $n = 16$) to 3.54 mmol/1.73 m^2 per day (SD 1.3; mean increase +65.8%, $n = 16$) at M3, to 5.09 (2.6; +138.7%, $n = 15$) at M12, and to 5.88 mmol/1.73 m^2 per day (5.7; +176%, $n = 12$) at M18. The highest increase was reached after the 5th dose with Uglyc of 7.47 mmol/1.73 m^2 per day (4.6, $n = 16$) and a mean increase of 250%. Mean Uglyc was lower in the VB6 group; however, percent increase over time was higher here (Table 2, Figure 1c and d).

Mean Ucit declined (Table 2, Figure 1e) from 1.78 (1.3, $n = 16$) to 1.56 (1.3, −12% $n = 16$) mmol/1.73 m^2 per day at M3. At M18, Ucit significantly declined by 34.5% (1.16 mmol/1.73 m^2 per 24h, SD 0.9, $n = 12$) as compared to baseline even though alkali medication was increased, when necessary (Table 1). Mean Ucit was in the normal range only in the non-VB6 group, but it dropped massively (from 2.74 to 1.42, −55.6%, $n = 4$) at M18 (Table 2). The lowest values over time were those in the VB6 patients. Of note, women showed lower Ucit, than men, and in VB6-treated women, Ucit kept constantly below normal (Supplementary Figure S2). In addition, Ucit strongly correlated with Uox ($n = 170$, r = 0.449, $P < 0.001$) (Figure 1f), and with Pcit ($n = 109$, r = 0.399, $P < 0.001$) (Supplementary Table S2).

Mean Pox was comparable to baseline over time (Table 2), but Pglyc significantly increased compared to baseline at M12 and M18 (Table 2, Figure 2a and b). This increase of Pglyc was significant at every timepoint

Table 2. Urinary and plasma parameters of patients with preserved kidney function and treated with the same lumasiran dose regimen

	Before treatment	Post monthly dosing (M3)	Post 1 yr (M12)	At 1.5 yrs (M18)
Urine and plasma parameters	Mean (SD, *n*)	Mean (SD, *n*)/percent change	Mean (SD, *n*)/percent change	Mean (SD, *n*)/percent change
All patients				
Uox	1.88 (0.8, 16)	0.73 (0.3, 16)/−61.3%[a]	0.72 (0.3, 15)/−61.8%[a]	0.65 (0.2, 12)/−65.7%[a]
Uglyc	2.13 (2.3, 16)	3.54 (1.3, 16)/65.8%[b]	5.09 (2.6, 15)/138.7%[a]	5.88 (5.7, 12)/176%[c]
Ucit	1.78 (1.3, 16)	1.56 (1.3, 16)/−12.1%[d]	1.88 (1.6, 15)/5.8%[d]	1.16 (0.9, 12)/−34.5%[c]
Pox	10.48 (4.1, 14)	6.96 (4.1, 11)/−34.6%[e]	9.31 (3.6, 12)/−12.6%[d]	9.9 (3.6, 10)/−7.0%[d]
Pglyc	48.82 (53.9, 14)	85.43 (46.8, 11)/75%[e]	315.8 (302.8, 12)/547%[c]	240.9 (174, 11)/393.5%[a]
Pcit	90.3 (37.5, 11)	69.8 (39.2, 9)/−22.7%[d]	92.9 (42.5, 11)/2.9%[d]	102.3 (33.1, 10)/13.4%[d]
eGFR	70.8 (23.0, 16)	70.4 (22.4, 15)/−0.56%[d]	73.2 (20.1, 15)/+3.4%[b]	78.2 (26.4, 12)/+10.5%[b]
VB6				
Uox	1.50 (0.5, 11)	0.67 (0.2, 11)/−55.6%[a]	0.73 (0.4, 10)/−51.4%[a]	0.60 (0.2, 8)/−59.8%[a]
Uglyc	1.43 (1.4, 11)	3.24 (1.3, 11)/126.6%[c]	3.9 (1.4, 10)/172.9%[b]	3.65 (2.8, 8)/155.7%[e]
Ucit	1.34 (1.0, 11)	0.95 (0.8, 11)/−29.5%[e]	1.65 (1.9, 10)/23%[d]	1.04 (1.0, 8)/−22.8%[b]
Pox	8.87 (3.3, 9)	7.61 (5.4, 6)/−18.1%[d]	8.99 (3.7, 7)/−3.2%[d]	8.87 (3.7, 7)/−4.5%[d]
Pglyc	23.7 (19.1, 9)	81.67 (57.2, 6)/244%[b]	420.4 (364.6, 7)/1671%[c]	172.39 (168.9, 7)/626.3%[b]
Pcit	95.9 (39.4, 8)	52.0 (25.5, 6)/−45.8%[d]	85.1 (38.8, 7)/−11.2%[d]	89.8 (30.6, 7)/−6.3 %[d]
eGFR	70.6 (25.5, 11)	71.4 (25.2, 11)/+1.1%[d]	71.1 (23.3, 10)/+0.7%[d]	74.1 (27.7, 8)/+5%[d]
Non-VB6				
Uox	2.72 (0.6, 5)	0.86 (0.3, 5)/−68.3%[b]	0.70 (0.2, 5)/−74.4%[e]	0.73 (0.2, 4)/−73.14%[e]
Uglyc	3.68 (3.1, 5)	4.19 (1.0, 5)/13.9%[d]	7.47 (3.1, 5)/103.1%[b]	10.35 (7.8, 4)/181.1%[e]
Ucit	2.74 (1.4, 5)	2.92 (1.3, 5)/−6.6%[d]	2.34 (0.3, 5)/−14.6%[d]	1.42 (0.8, 4)/−55.6%[e]
Pox	13.38 (4.1, 5)	6.19 (1.9, 5)/−53.7%[e]	9.77 (3.8, 5)/−27.0%[d]	12.31 (1.9, 3)/−8.0%[d]
Pglyc	93.98 (68.9, 5)	89.94 (36.5, 5)/−4.3%[d]	169.4 (82.5, 5)/80.2%[d]	360.93 (116.8, 4)/284.0%[e]
Pcit	75.4 (33.8, 3)	105.5 (40.9, 3)/40%[d]	106.6 (51.3, 4)/41.4%[d]	131.5 (17.6, 3)/74.5%[d]
eGFR	71.3 (18.8, 5)	67.6 (14.6, 4)/−5.2%[d]	77.6 (16.1, 5)/+8.8%[d]	86.4 (25.4, 4)/+21.2%[e]

eGFR, estimated glomerular filtration rate; Pcit, plasma citrate; Pglyc, plasma glycolate; Pox, plasma oxalate; Ucit, urinary citrate; Uglyc, urinary glycolate; Uox, urine oxalate; VB6, vitamin B6.
Mean urinary oxalate excretion (Uox, mmol/1.73 m^2 per 24h), mean urinary glycolate excretion (Uglyc, mmol/1.73 m^2 per 24h), mean urinary citrate excretion (Ucit, mmol/1.73 m^2 per 24h), mean plasma oxalate concentration (Pox in μmol/l), mean plasma glycolate concentration (Pglyc in μmol/l), mean plasma citrate concentration (Pcit, in μmol/l), mean estimated glomerular filtration rate (eGFR, ml/min per 1.73 m^2), standard deviation and sample size (SD, *n*) and mean percent reduction or increase from baseline in all patients who collected 24-hour urine and treated with lumasiran 3 mg/kg monthly during first 4 doses, then quarterly, as well as in groups treated with vitamin B6 medication (VB6) or without (non-VB6).
Paired Wilcoxon test at every time point compared to baseline:
[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] not significant.
[e] $0.1 < P < 0.05$.

analyzed in VB6, but not in non-VB6 (Figure 2c and d). Pcit decreased from baseline to M3 (−22.7%), which was primarily the case in the VB6 group (−45.8%) (Table 2 and Supplementary Figure S2). At end of follow-up, Pcit was back to values equivalent to before treatment. Overall, there was a significant increase in estimated glomerular filtration (Table 2, +10.5% at M18), which was more pronounced (near significant) in the non-VB6 group (+15.4 ml/min, +21.2 %).

We found significant correlations when comparing all parameters with each other (Uox, Uglyc, Pox, Pglyc, and Pcit), the strongest being for Pglyc and Uglyc, and for Pglyc and Pcit (Supplementary Table S2 and Supplementary Figure S3). Four infants (P17–P20) received lumasiran with another dosing regimen. Their Uox/creatinine ratios declined, reached normal/near normal in 2 (P19 and P20) but fluctuated in the other 2 (P17 and P18) (Supplementary Table S1). Uglyc/creatinine ratios were high at baseline in 3, normal in 1, but increased or remained elevated during the whole period of treatment.

In addition, we observed serum lactate above 2.2 mmol/l in 4 patients; however, in general, a decline in Ucit, which made an adaptation of alkali treatment necessary (Tables 1 and 2).[36] In 2 of 4 patients, serum lactate was already elevated before treatment, when they presented with lactic acidosis and acute kidney failure. Because diagnosis was unclear then, no Pox or Pglyc were measured.

Stones and/or nephrocalcinosis were found in all patients at baseline, with the exception of P20 who received lumasiran since 2nd day of life and ultrasound was normal. In 1 patient each, nephrocalcinosis progressed (P17), or ameliorated (P19). In all other, it remained stable. In 6 patients, either a new stone was found in ultrasound (P4), spontaneous stone passages took place, or stone removal procedures were necessary (P1, P6, P12, P14, and P16). In P1 and P6, stone size increased during treatment, even though Uox normalized in P1 (Table 1, Supplementary Table S1). These 2 and P14 needed extensive stone removal procedures.

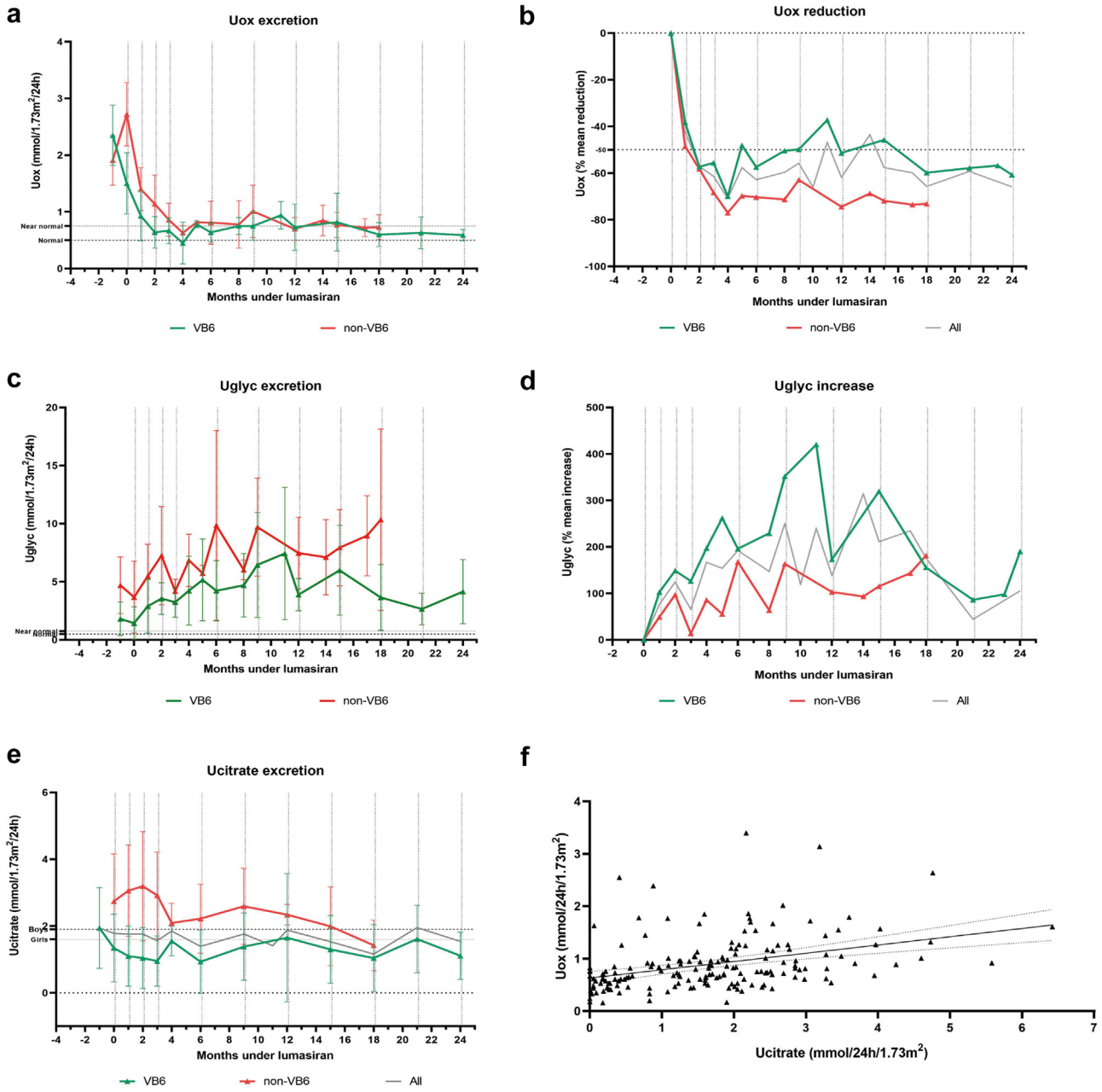

Figure 1. Urinary parameters in patients with preserved kidney function and treated with 3 mg/kg lumasiran monthly for the induction phase, and then quarterly: (a–e) Follow-up of urinary oxalate (Uox), glycolate (Uglyc), and citrate (Ucit), as well as percent reduction of Uox and percent increase in Uglyc, whole group and related to treatment or no treatment with vitamin B6 (VB6). Every point depicts mean (± SD) of $n \geq 3$. (f) correlation of Uox/Ucit excretion.

Lumasiran medication was increased in P2 after 24 months from 3 to 4.5 mg/kg body weight quarterly, and it is planned for P6 and P7. Medication was stopped in 3 other patients (P1, P5, and P14). P1 suffered from severe injection side pain and developed an aggressive behavior, for which he received psychological treatment. The parents requested to stop medication. P5 asked to finish medication being now more compliant to VB6 medication and in P14, Uox did not change (Supplementary Table S1), and the clinical situation remained unfavorable (Table 1).

Patients on Dialysis

Median follow up of the 13 patients on dialysis was 15 months. In those treated with 3 mg/kg monthly (or 6 mg/kg according to age) for the first 4 months and then quarterly (P21, 22, 24–28, 30, and 33), mean Pox decreased significantly from 78 (SD 40.2, $n = 9$) to 37.2 µmol/l (16.9, $n = 9$; mean decrease −52.4%) at M3, increased again to 43.1 (16.3, $n = 6$; −44.7%) at M12, and to 59.3 µmol/l (23.8, $n = 3$; −24 %) at M18 (Table 3, Figure 3a and b). This course in Pox was not different when related to VB6, however, the non-VB6

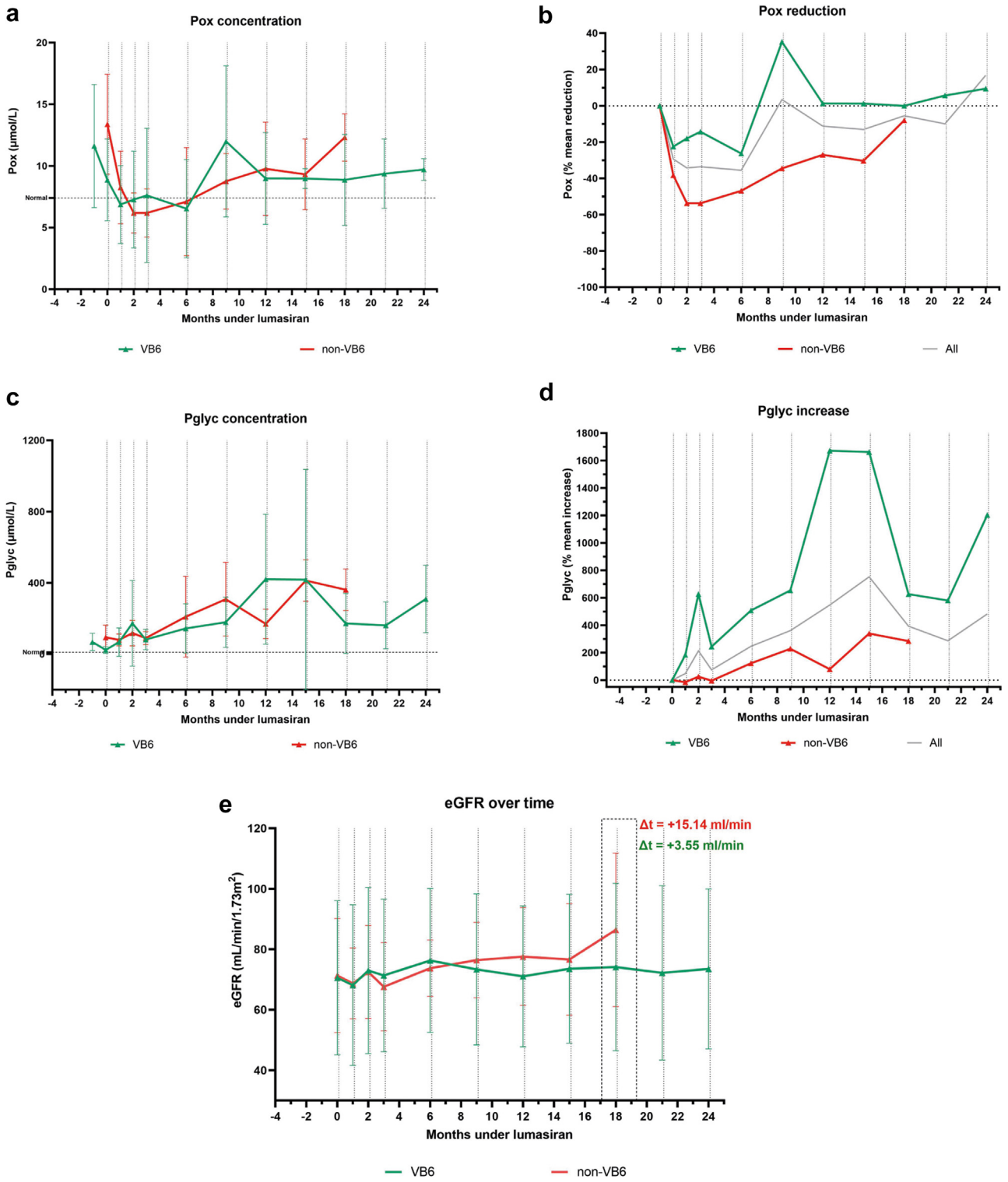

Figure 2. Plasma parameters in patients with preserved kidney function and treated with 3 mg/kg lumasiran monthly for the induction phase, and then quarterly: Follow-up of plasma oxalate (Pox) (a) and plasma glycolate (Pglyc) (c), as well as percentage reduction of Pox (b) and percentage increase of Pglyc (d), whole group and related to treatment or no treatment with vitamin B6 (VB6). Every point depicts mean (± SD) of $n \geq 3$. (e) Estimated glomerular filtration rate over time of lumasiran treatment, and according to VB6 medication; Δt depicts the eGFR change after 18 months of treatment, as compared to baseline. eGFR, estimated glomerular filtration rate.

patients had higher Pox (Table 3, Figure 3). In VB6 sensitive P24 and P28, Pox declined below supersaturation, and they were then successfully transplanted.

Mean Pglyc increased significantly over time from 216.4 (SD 210.8, $n = 8$) to 337.4 µmol/l (294.6, $n = 8$; mean increase 55.9%) at M3, to 443.3 (638.3, $n = 6$; 104.8%) at

Table 3. Plasma parameters of patients on dialysis and treated with lumasiran with dose regimen according to age

	Before treatment	Post monthly dosing (M3)	Post one yr (M12)	At 1.5 yrs (M18)
Plasma parameter	Mean (SD, *n*)	Mean (SD, *n*)/percent change	Mean (SD, *n*)/percent change	Mean (SD, *n*)/percent change
All patients				
Pox	78.0 (40.2, 9)	37.2 (16.9, 9)/−52.4%[a]	43.1 (16.3, 6)/−44.7%[b]	59.3 (23.8, 3)/−24.0%[c]
Pglyc	216.4 (210.8, 8)	337.4 (294.6, 8)/55.9%[d]	443.3 (638.3, 6)/104.8%[b]	259.5 (271.0, 3)/19.9%[c]
Pcit	342.8 (550.4, 6)	151.6 (202.8, 6)/−55.8%[c]	99.2 (45, 6)/−71.1%[n.s.]	88.4 (18.8, 3)/−74.2%[c]
VB6				
Pox	67.3 (39.9, 6)	27.1 (5.3, 6)/−59.8%[d]	39.6 (15.4, 5)/−41.2%[b]	$n = 2$ patients only
Pglyc	84.4 (52.9, 5)	253.1 (257.2, 6)/199.8%[b]	191.2 (180.8, 5)/126.5%[c]	$n = 2$ patients only
Pcit	113.1 (55.5, 3)	62.6 (26.8, 4)/−44.7%[c]	90.7 (44.7, 5)/−19.8%[c]	$n = 2$ patients only
Non VB6				
Pox	99.4 (38.1, 3)	57.4 (12.2, 3)/−42.2%[c]	$n = 2$ patients only	$n = 2$ patients only
Pglyc	436.4 (183.9, 3)	$n = 2$ patients only	$n = 1$ patients only	$n = 1$ patients only
Pcit	572.6 (772, 3)	$n = 2$ patients only	$n = 1$ patients only	$n = 1$ patients only

Pcit, plasma citrate; Pglyc, plasma glycolate; Pox, plasma oxalate; VB6, vitamin B6.
Mean plasma oxalate concentration (Pox, µmol/l), mean plasma glycolate concentration (Pglyc, µmol/l), mean plasma citrate concentration (Pcit, µmol/l), standard deviation and sample size (SD, *n*) and mean percent reduction or increase in patients on hemodialysis treated with lumasiran 3 mg/kg (or 6mg/kg according to age) monthly during first 4 doses, then quarterly, as well as in groups treated with vitamin B6 medication (VB6, all under 3mg/kg lumasiran) or without (non-VB6, all under 6 mg/kg lumasiran).
Paired Wilcoxon test at every time point compared to baseline:
[a] $P < 0.01$.
[b] $0.1 < P < 0.05$.
[c] not significant.
[d] $P < 0.05$.

M12 and decreased to 259.5 µmol/l (271, $n = 3$; 19.9%) at M18 (Table 3, Figure 3c and d). In VB6-sensitive patients, mean Pglyc was highest after monthly dosing (Table 3).

We observed Pglyc values of 1 to 4 mmol/l in 6 patients and elevated serum lactate values especially in P23 with 6.93 mmol/l at the highest.

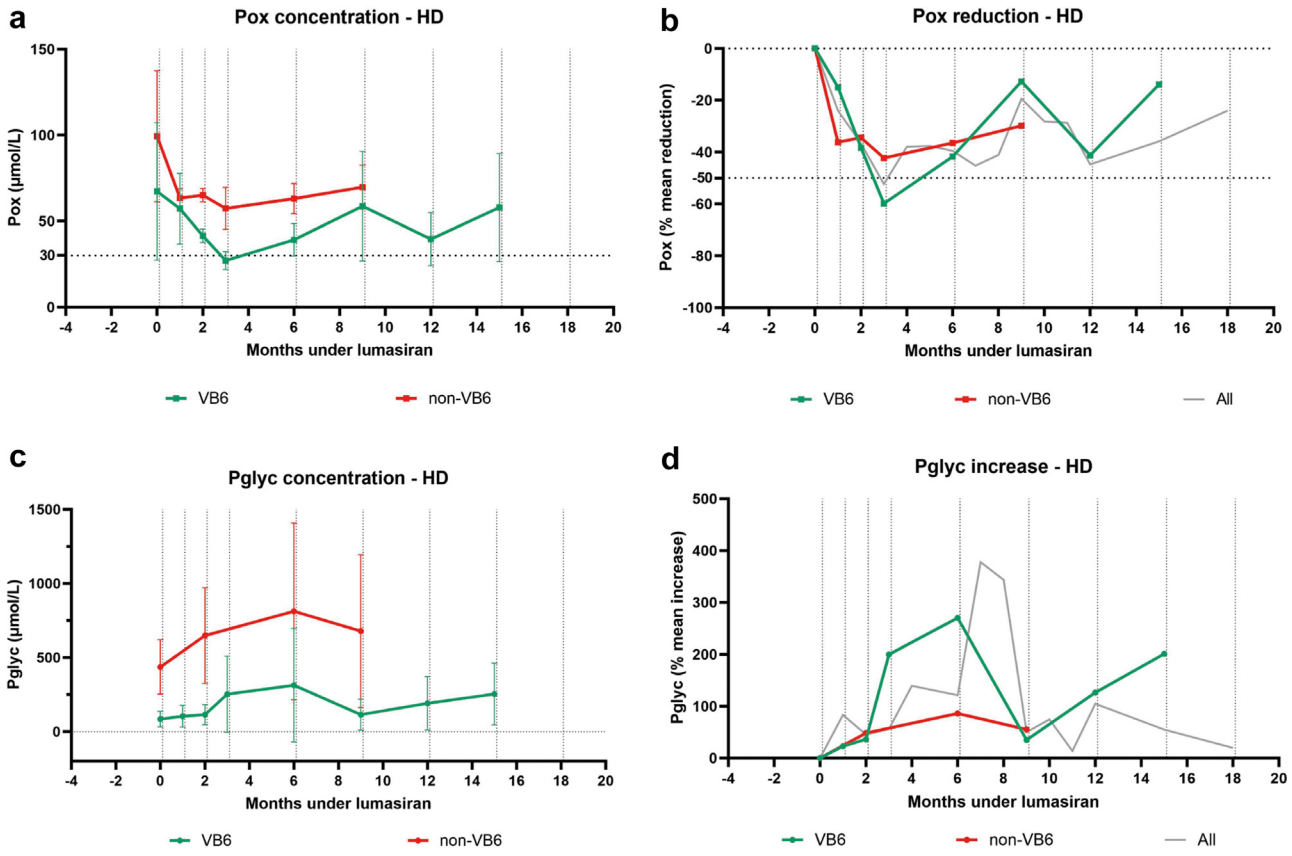

Figure 3. Plasma parameters in patients with dialysis and treated with 3 mg/kg (or 6mg/kg according to age) lumasiran monthly for the induction phase, and then quarterly: Follow-up of plasma oxalate (Pox) (a) and plasma glycolate (Pglyc) (c), as well as percentage reduction of Pox (b) and percentage increase of Pglyc (d), whole group and related to treatment or no treatment with vitamin B6 (VB6, all of them treated with 3 mg/kg lumasiran). Every point depicts mean (± SD) of $n \geq 3$. HD, hemodialysis.

Pox and Pglyc did not change in 1 VB6-sensitive patient (P22), and lumasiran was stopped after M22. His speckle and bone MRI exams did not show a progression of oxalate deposition. Pox and Pglyc remained stable after stopping lumasiran and patient was placed on the isolated kidney transplantation waiting list.

In the patient on PD (P29), Pox and Pglyc fluctuated over time (Supplementary Table S1), however, Pox increased from 41.6 μmol/l before lumasiran to 83.42 before the 9th dosage (highest value). In addition, Pglyc increased from 14.9 μmol/l to 777.9 μmol/l. The highest Pglyc was seen between 7th and 9th dosage peaking at 2062.5 μmol/l. Clinically, the patient's nutritional and cardiac status improved,[29] less doses of erythropoietin were needed, and no hospital admissions or major complications appeared.

Bone MRI performed in 5 patients on HD did not show amelioration, except in P23 (Figures 4 and 5). A bone biopsy performed in one of the patients (P21) at M12 of treatment showed huge amounts of bony oxalate, nicely related to the bone MRI result. In the patient with the lowest Pox value (P24), we did not find systemic oxalosis, even though being on dialysis in the past 8 years and on VB6 5 years before lumasiran. Isolated kidney transplantation was later performed. With normalized Uox after transplantation, lumasiran treatment was stopped at M21.

P23, who received a dosage of 4.5 mg/kg, developed lactic acidosis. Pox fluctuated, and overall did not decrease; Pglyc increased dramatically and peaked at 4 mmol/l. Here, serum lactate levels were at the highest with approximately 7 mmol/l. The clinical situation first deteriorated, and the patient was unable to walk, correlating to a disastrous bone MRI (Figure 5). At M20, bone MRI showed a slight amelioration, which correlated with the patient starting to walking again. The patient died at M24 unrelated to lumasiran treatment.

In P28, HD was started early to avoid overt systemic oxalate depositions. Pox declined over time below saturation threshold (Supplementary Table S1). The patient then received a successful liver/kidney transplantation at M8 of treatment; therefore, lumasiran was withdrawn.

In 2 patients on HD with infantile oxalosis (P31 and P32), retinal oxalate depositions were diagnosed before lumasiran treatment, which progressed until M6, and then remained unchanged (Figure 6). At last follow-up (M14) Pox had decreased in both. Pglyc remained elevated and peaked between the 7th and the 9th injections.

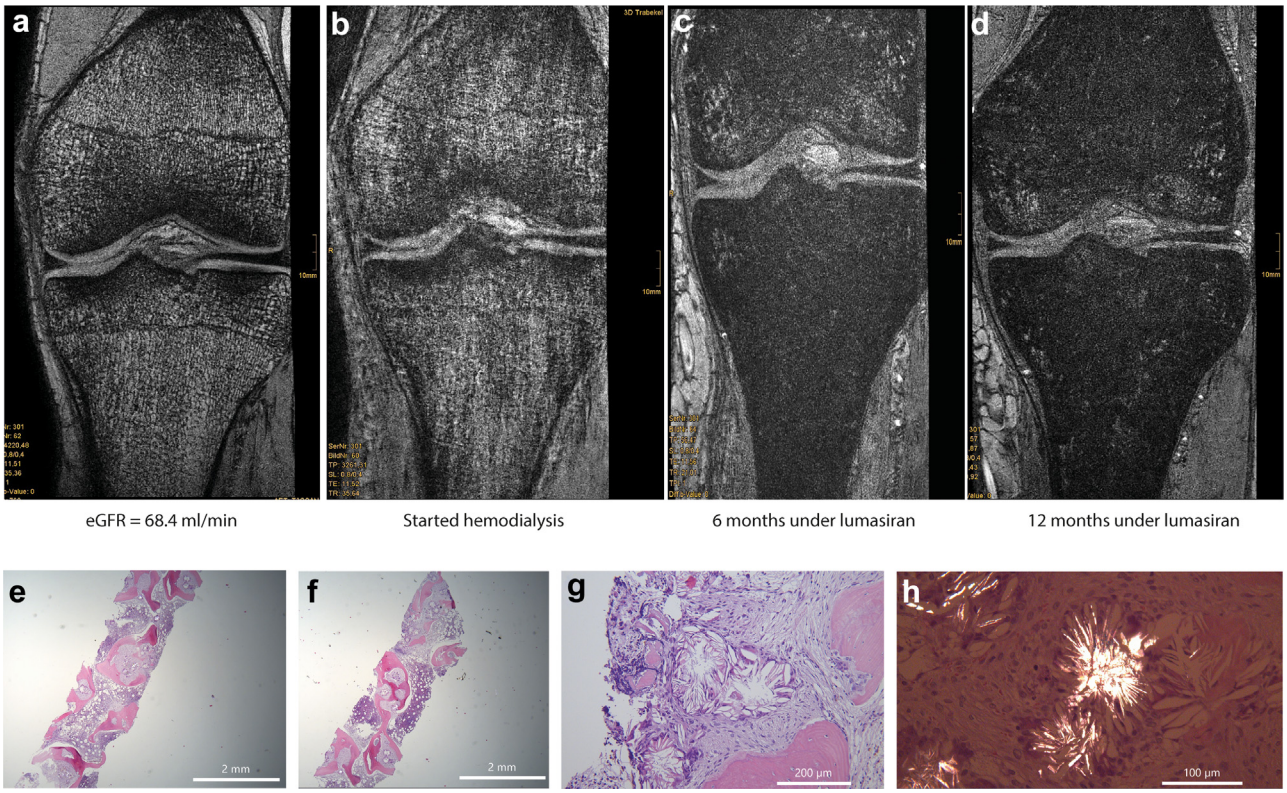

Figure 4. Systemic oxalosis analysis in P21. MRI on bone (a–d) at 27 years old and eGFR 68.4 ml/min (a), at starting hemodialysis (b), and 6 months (c), and 12 months (d) after starting lumasiran treatment. Bone biopsy (e–h) stained with hematoxylin-eosin and analyzed under light microscope (e–g) and polarized light (h) revealed 50% fibrosis and a significant number or birefringent calcium-oxalate crystals at time of last MRI (d). eGFR, estimated glomerular filtration rate.

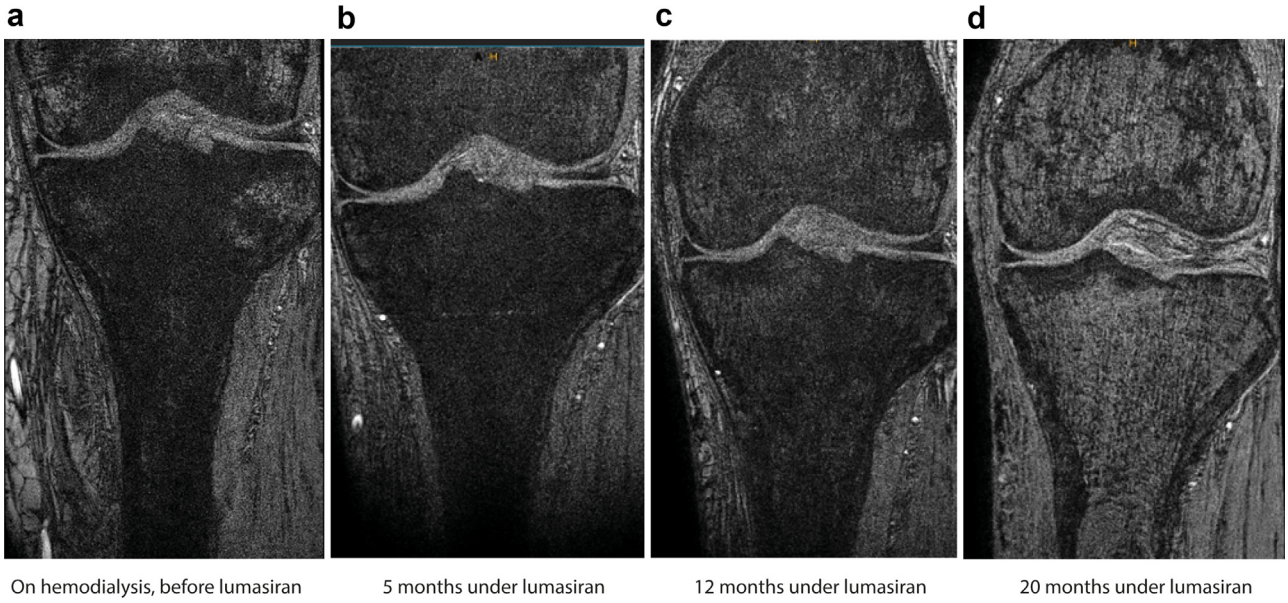

Figure 5. Systemic oxalosis analysis in P23. Bone MRI before starting (a), and after 5 months (b), 12 months (c), and 20 months (d) of lumasiran treatment.

As mentioned, lumasiran medication was stopped in 3 patients on HD (P22, P24, and P28). Dosing interval in P26 was changed from quarterly to bimonthly 6 mg/kg body weight per dose. P31 and P32 now receive 47.25 mg/dose every other month, both with a body weight of 11 kg, corresponding to the dose of 6 mg/kg quarterly.

DISCUSSION

Lumasiran is safe in patients with preserved kidney function and in those on dialysis. In preserved kidney function, Uox decreased in most of the patients, and Uglyc increased. In quarterly dosing, not all patients showed a sustained reduction in Uox excretion; therefore, application might be individually adapted to avoid oxalate spiking especially at the end of every quarterly dosing. Moreover, determining whether a patient has concomitant VB6 medication is necessary to properly evaluate treatment efficacy. In patients on dialysis, Pox did not decrease over time, but Pglyc increased significantly. In both groups, alkaline need was increased. This may be related to elevation of glycolate production under lumasiran treatment, which definitively needs more investigation.

The introduction of RNAi medication(s) was much appreciated because it was expected to be a quantum leap in treatment of PH1. Normalization or near

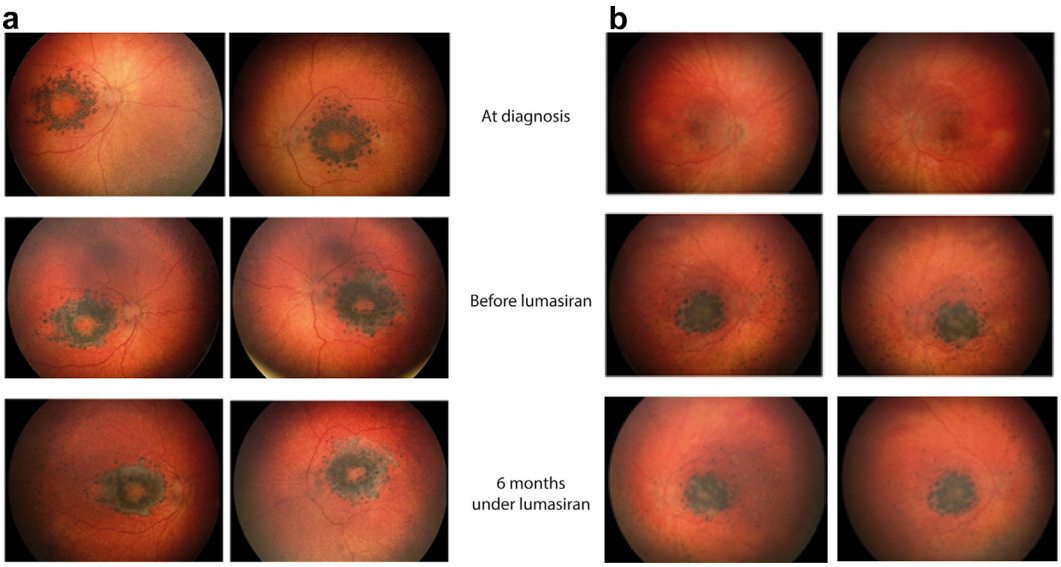

Figure 6. Systemic oxalosis analysis in P31 (a) and P32 (b). Eye examination by fundoscopy revealed bilateral calcium oxalate deposits in both patients at diagnosis, shortly before starting lumasiran, and 6 months after starting the medication.

normalization of Uox should lead way to no or at least less kidney stones, no nephrocalcinosis, no kidney failure, and no necessity for transplantation in the patients diagnosed and treated early.

In patients with preserved kidney function, lumasiran effectively reduces Uox in most patients. Patients who are VB6-sensitive, and thereby reach normal Uox and Uglyc, are obviously not in need of an extremely expensive newer medication. Therefore, VB6 medication should promptly be used and tested for effectiveness, with the exception of clearly nonsensitive *AGXT* variants, before RNAi medication is considered.[8] If VB6 works, it may work better than RNAi because it also reduces Uglyc and Pglyc. Medication efficacy should be interpreted based on excretion from 24-hour urines (when possible), because creatinine ratios may underestimate the urinary elimination of oxalate.[37] In addition, efficacy as percent reduction from baseline may not really show the true response of a patient.

It was apparent that monthly dosing reduces Uox but increases Uglyc. In patients with preserved kidney function, Pox remains stable, but Pglyc increases, obviously leading not to dangerous levels, but to more alkali need. When switching to quarterly dosing, this dosing interval is not sufficient in all patients. Already, after the first quarterly interval, patients showed clearly elevated Uox values again at end of the dosing period (P3, P4, P6, P7, P10, and P13). In addition, Uglyc was increasing, as was Pglyc and both were nicely correlating to each other, indicating a much better elimination of glycolate, as compared to oxalate, thus less systemic glycolate deposition.

The increase in Uox in the second half of the quarterly dosing interval puts our patients on risk again. Six patients either had new stone developments or needed stone removal procedures. In addition, contrary to the Illuminate study data,[15] we could not find evidence that nephrocalcinosis grading ameliorated in general. Kidney function stabilized or even ameliorated as expressed by a significant increase in estimated glomerular filtration from baseline to M18. Because this was more pronounced in the non-VB6 group, this increase expresses best the lumasiran effect on protection of kidney function.

In patients on HD/PD, Pox is not a sufficient parameter of treatment success, especially in patients with systemic oxalosis in whom imaging studies have to be added. However, in patients without systemic oxalate depositions, Pox declined, so that they could be transplanted. In addition, the clinical situation of the patient on PD ameliorated. We did not observe a therapeutic effect in 1 patient on HD and can only speculate about the reasons, for example, antibodies against lumasiran or inadequate binding to *HAO1* mRNA. *HAO1* was completely sequenced in this patient, including the small interfering RNA binding site in the 3′ UTR, though no variant was detected. An increase in Pglyc, development of acidotic metabolic states and need of (more) alkalinization has to be considered, checked, and corrected when necessary. However, the underlying mechanisms are unclear and definitively need further investigation.

If we would consider reduction of Pox to be necessary to prove treatment efficacy in dialysis, current dosing would be regarded sufficient only in patients without overt systemic oxalosis. It is speculative on whether monthly dosing would be the better option in all others, because mean Pox first decreased and increased again in quarterly dosing. Nevertheless, patients P30 to P32 had monthly dosing and their Pox values decreased concomitantly; however, their Pglyc values also reached >1 mmol/l concentrations. This makes clear that Pglyc levels need to be checked on a regular basis.

By including imaging procedures in our routine follow-up, we had recognized that the missing decline in Pox could be related to the dissolving of calcium-oxalate from various body tissues.[33] Therefore, the fluctuation of Pox values was attributed to the amount of oxalate being deposited systemically before treatment. For that reason, though, we would now have expected much more clinical improvement of systemic oxalosis by means of bone MRI and cardiac speckle. Nevertheless, at least in the patient on PD, we saw an amelioration of the clinical symptoms and secondary parameters such as reduction in erythropoietin dosage let us speculate that oxalate osteopathy declined.

We noted that stopping or reduction of concomitant medication (VB6 and citrate) and/or hyperhydration is not advisable. This is especially true for patients in whom Uox only declined to normal with concomitant VB6 medication. We also observed in patients on HD, that a combination of RNAi and VB6 achieved a lower Pox, but a significantly lower increase in Pglyc. The latter should no longer be regarded completely harmless, as we experienced Pglyc values >1 mmol/l in 6 patients, 1 of them showing lactic acidosis going along with an elevation of glycolate in plasma. The others were buffered with daily HD and thus more alkali treatment. In addition, in patients with preserved kidney function, the decrease in Ucit may express more alkali need because of an increase in Pglyc.

Dosing intervals may need to be personalized, because patients may need monthly or 2 monthly dosing, or an increase in dosing in quarterly regimens. This increases expenses dramatically and it will also increase the risk of an acid overload with increasing Pglyc over time. Therefore, we recommend to always check for an acidic

metabolic state even when measuring glycolate is not possible. A surrogate parameter here indeed may be Ucit.

Finally, there are patients with preserved kidney function and without systemic oxalosis, who did not show a reduction of Uox to normal or near normal. The reason for that is currently speculative. Because Uglyc was increasing, the medication is working, so that an increase in dosage may be necessary and is now provided. Up until now, only some patients were cotreated with the other RNAi medication, nedosiran,[38] or stiripentol,[18,25] both blocking liver specific LDHA, the final step of oxalate production.[39] There is, though, not enough information yet to compare results. If such a procedure would really be helpful, the extreme socioeconomic burden needs to be taken into consideration.

Before combined transplantations are skipped, it has to be clearly demonstrated, that lumasiran or any other medication really reduces Pox in patients with no or less systemic oxalosis, or leads way to significant reduction of systemically deposited oxalate in the other. Reduction of systemic oxalate deposition will need a long time and intensified HD treatment, which will then be burdensome or even problematic in small infants before isolated kidney transplantation is possible. P30 to P33 were on the waiting list for combined transplantation, because they had catheter-related problems, which made HD very difficult. In addition, oxalate removal with HD is still minor to oxalate removal after liver and kidney transplantation, or RNAi and kidney transplantation alone. In the meantime, P30, P31, and P32 received successful liver and kidney transplantation.

We acknowledge the limitations of our research. The data reported is real world data and not achieved during a clinical study with strict regulations. Decisions were taken locally based on the treating physician's choice and country-specific policies. The follow-up procedures are different between centers and therefore, not all data points are equal or even collected. For that reason, some points are missing, and the number of patients is sometimes too low to adequately provide statistical significance in our results. In addition, we did not set a decision timing for assessing lumasiran efficacy in advance; for that reason, we cannot suggest the best time point to interpret efficacy and thus continuation or not of the medication.

In summary, lumasiran is efficacious in reducing Uox in patients with preserved kidney function and in decreasing Pox in patients on HD without overt systemic oxalosis. However, adaptation of dosing regimens may be needed in a subgroup of patients. In HD/PD, longer treatment periods may prove efficacy by imaging analysis and decline in Pox. Acid-base status has to be checked to avoid acidic metabolic states in patients with overt increases in Pglyc. Increases in alkali medication may thus be helpful.

DISCLOSURE

BH and CM-H are consultants to Dicerna/Novo Nordisk. BH is a consultant to Avanzanite and Arbor Biotech. CM-H, MPB, and BBB received consulting fees from Alnylam Pharmaceuticals. CJS has received honoraria from Alnylam and Genesis Pharma. CPS has received research funding (investigator initiated studies) from Baxter, advisory fees from Baxter and lecturing honoraria from Fresenius. All other authors declare no competing interests.

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AUTHOR CONTRIBUTIONS

All authors collected the data from their own patients and provided clinical and historical information for Table 1. BH and CM-H wrote the paper and performed statistical analysis. AW did all laboratory analysis. All authors proofread the paper and accepted it for publication.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1. Flow chart of patients follow-up.

Figure S2. Urinary citrate excretion in all females and males, and plasma citrate in patients with preserved kidney function and according to VB6 medication.

Figure S3. Correlation analysis of urinary oxalate (Uox), urinary glycolate (Uglyc), plasma oxalate (Pox), plasma glycolate (Pglyc), and plasma citrate (Pcit) with each other.

Table S1. Individual data per patient on urinary oxalate (Uox), urinary glycolate (Uglyc), plasma oxalate (Pox), plasma glycolate (Pglyc), plasma citrate (Pcit), urinary citrate (Ucit), bicarbonate (HCO3-), base excess, serum lactate, serum vitamin B6, pH, estimated glomerular filtration rate (eGFR), and primary hyperoxaluria-related medication.

Table S2. Correlation analysis of urinary citrate (Ucitrate) with urinary oxalate (Uox), urinary glycolate (Uglyc), plasma oxalate (Pox), plasma glycolate (Pglyc), and plasma citrate (Pcit).

Strobe Statement.

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