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A Targeted Release Capsule of Lanthanum Carbonate: a New Efficient Cheap Treatment for Primary Hyperoxalurias

Marc E. De Broe[1], Marc P. Uytterhoeven[2], Jan De Causmaecker[3], Yannick De Brucker[4], Erik D. Snelders[5,6], Johan Van De Walle[7], Koen Van Hoeck[6,8], Dominique Trouet[6,8] and Monique Elseviers[9]

[1]Laboratory of Pathophysiology, University of Antwerp, Wilrijk, Belgium; [2]Sonic Healthcare Benelux AML, Antwerp, Belgium; [3]Pharmacist, Lokeren, Belgium; [4]Department of Radiology, Vrije Universiteit Brussels, Ixelles, Belgium; [5]Department of Nephrology, Antwerp University Hospital, Edegem, Belgium; [6]Laboratory of Experimental Medicine and Pediatrics (LEMP), University of Antwerp, Wilrijk, Belgium; [7]Department Pediatric Nephrology, Ghent University Hospital, Ghent, Belgium; [8]Department Pediatric Nephrology, Antwerp University Hospital, Edegem, Belgium; and [9]Center for Research and Innovation in Care, University of Antwerp, Antwerp, Belgium

Introduction: Primary hyperoxaluria (PH) is a devastating disease in children and adults. Recently, a substantial progress in the treatment of this deadly disease has been made that consists of the introduction of the RNA inhibitors, lumasiran and nedosiran, which deplete the substrate for oxalate synthesis.

Methods: Lanthanum carbonate (Lanth.Carb., $La^2[CO_3]^3$) is a powerful phosphate binder having a strong affinity to oxalate. Its use as such in PH is not relevant because patients with normal renal function develop a severe phosphate depletion without a clear effect on oxalate balance. Considering that the absorption of phosphate is in the early gastrointestinal (GI) tract and mainly in the distal part of the GI tract for oxalate, we developed a targeted release capsule (trc) containing 500 mg Lant.Carb. released in the distal part of the GI tract as proven by radiological investigations of the radiopaque trcLanth.Carb.

Results: Four patients with PH and estimated glomerular filtration rate $>$ 60 ml/min per 1.73 m^2 were treated with trcLanth.Carb., which turned out to decrease the urinary oxalate concentrations clearly $<$ 0.51 mmol/24 h per 1.73 m^2,45 mg/24 h per 1.73 m^2 (considered as upper limit of normal), after 2.5 months of treatment in 3 patients and 18 months in 1 patient. Calciuria remained normal or decreased slightly. Phosphaturia and phosphatemia remained normal and stable in all 4 cases.

Conclusion: trcLanth.Carb. is a promising repurposed, efficient, nontoxic, and cheap drug, lacking serious side effects in the treatment of any type of PH in whatever place in the world. A randomized controlled trial supporting this proof-of-concept is the next step.

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KEYWORDS: primary hyperoxalurias; efficient; cheap; treatment; trc-Lanthanum Carbonate

PHs are rare inborn errors caused by autosomal recessive variants in 3 genes that encode enzymes involved in glyoxylate metabolism characterized by the overproduction of oxalate in the liver, which is poorly soluble and deposited as calcium oxalate (CaOx) in various organs in patients with PH. The increased production in the liver results in increased urinary excretion of oxalate, which in association with calcium results in CaOx crystal formation leading to renal stones, kidney failure, and in some cases dialysis or transplantation.[1-3] In view of their low prevalence (1–3/million inhabitants in the European area), PHs are classified as orphan diseases (Supplementary Text S1 "Prevalence"). In countries with high consanguinity rates, such as North African and Middle Eastern populations, the prevalence of PHs is clearly higher, with 10 cases per million inhabitants and even more (underdiagnosis).[3,4]

In addition, in developing countries, where the disease is most prevalent and underdiagnosed, there are many challenges in PH diagnosis and management, with economic constrains and ethical concerns. This has led to the existing gap in the management of PH between developed and developing countries, which is expected to further deepen with the advent of novel therapeutic agents unless appropriate actions are taken.[4]

Correspondence: Marc E. De Broe, Hillare 12, B-9160 Lokeren, Belgium. E-mail: marc.debroe@uantwerpen.be
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Increasing the daily intake of water (up to 2–3 l/24 h per 1.73 m^2 or more) when possible, trying to obtain a urinary concentration < 0.51 mmol/24 h per 1.73 m^2, 45 mg/24 h per 1.73 m^2 oxalate, is probably the most important immediate measure in young patients. Alkalinization with potassium citrate can reduce urinary CaOx saturation by forming soluble complexes with calcium, thus decreasing stone formation.[3]

Food with high oxalate content is restricted from their diet.[2] However, because by far, most of the oxalate in patients with PH is of endogenous source (liver synthesis), these dietary measures are of minor impact in most patients.

Pyridoxine is a coenzyme of alanine-glyoxylate aminotransferase that promotes the conversion of glyoxylate to glycine, rather than to oxalate. Ten percent to 30% of patients with PH type 1 will respond to pyridoxine therapy with a limited reduction of urinary oxalate excretion.[1,2]

Enhancing oxalate elimination by emptying the colon of oxalate by bacterial digestion[5] and the stimulation of the transport system of SLC26A, are potential methods to reduce tissue and body oxalate levels.[5] Unfortunately these promising results were not confirmed by multicenter trials.

All these measures have been used during many years with rather disappointing results, particularly in patients with severe forms of PH[1-5]

Very recently, a substantial progress in the treatment of this deadly disease has been made, which consists of the introduction of the inhibitors of RNA, lumasiran and nedosiran,[6,7] which deplete the substrate for oxalate synthesis. This interesting drug (lumasiran) can decrease the 24-hour urinary oxalate excretion to below the upper limit of normal of <0.51 mmol/24 h per 1.73 m^2, 45 mg/24 h per 1.73 m^2 in 52%[5] of the patients with PH, which is interesting but not effective enough in all cases.

Stiripentol is an antiepileptic drug used to treat children with Dravet syndrome; it has been shown to inhibit neuronal lactate dehydrogenase 5 enzyme. Because this isoenzyme is also the last step of hepatic oxalate production, stiripentol would potentially reduce hepatic oxalate production and urine oxalate excretion. *In vitro*, stiripentol decreased the synthesis of oxalate by hepatocytes in a dose-dependent manner. *In vivo*, oral administration of stiripentol significantly reduced urine oxalate excretion in rats. A randomized controlled trial is currently in the run.[8]

We started developing a trcLanth.Carb. capsule, a particular galenic form of lanthanum carbonate for the following reasons. When a powerful phosphate binder such as aluminum or Lanth.Carb. (Fosrenol) is given to patients with a normal or slightly decreased estimated glomerular filtration rate, a phosphate depletion is developed, ending in osteomalacia, while oxaluria remains stable or decreased slightly.[9-14] Intestinal absorption of oxalate is rather variable[15,16] (in 120 volunteers varying from 2.2%–18.5%) and dependent on the diet.[17,18] It is known that phosphate is mainly absorbed in the early part of the GI tract whereas oxalate is absorbed more in the distal part of it.[19,20] Chelating oxalate in the colon stimulates the transport system of SLC26A, increasing the secretion of oxalate from the serum toward the distal part of the GI tract, particularly in renal failure.[21-26]

Here, we report the production of a trcLanth.Carb. capsule containing Lanth.Carb. demonstrating the release of lanthanum in the distal part of the GI tract, and the efficacy of this capsule in the normalization of urinary oxalate in 4 patients with PH (types 1 and 3), while phosphaturia remains normal and stable.

METHODS

Development of the trc Lanthanum Carbonate

The preparation of an orally administrable pharmaceutical dosage form configured as a coated capsule 00 for targeted delivery to the distal part of the GI of a subject is as follows.

Gelatine capsules 00 were filled with the powder blend from the Lanth.Carb. (Solara Chennai-India) 500 mg per capsule, corresponding to 292 mg elemental lanthanum per capsule. A Drug Master File of Lanth.-Carb. was obtained from the company. Other compounds were corn starch 25 mg, stearate 10 mg, and pro 1 gelatine capsula. The weight of 1 gelatine capsula is 630 g. The capsules were coated; composition of the coating solution was Eudragit S 100: 10% (w/w) (Evonik Industries, Belgium), triethyl citrate: 1% (w/w) (Sigma Aldrich, Germany), and acetone 89% (w/w) (acetone extra pure, Fagron, The Netherlands). The coating solution was prepared by dissolving triethyl citrate (plasticizer) in acetone. Eudragit S 100 was gradually added while stirring on a magnetic stirrer until completely dissolved, which took between 1 and 2 hours. Filled capsules, size 00, were manually coated with Eudragit solution using a manual coater (Feton International, Belgium) according to the following steps: a first dipping of the body of the capsules, dipping and withdrawal time was 15 seconds; repeat dipping of the body of the capsule, up to 3 times. Finally, at the end of our testing, the pharmaceutical dosage form was prepared by performing a fourth coating step of the body with a coating configured for targeted delivery to the distal part of the GI tract of a subject.

Drying time between the layers was 5 minutes and the fourth layer was left to dry for 15 minutes. Prepared capsules were stored at room temperature between 20 °C and 24 °C.

X-ray Investigations

Lanthanum is a metallic chemical element with an atomic mass of 138.9; therefore it is radiopaque[26–30] and easily visible on X-ray images. With the use of serial X-ray imaging (Siemens Luminos drfMax, Erlingen, Germany) and ultra–low-dose computed tomography (CT, [ULDCT]) imaging (Canon Medical Systems Aquilion ONE, Tustin, CA) made in a supine position, the exact area of release of lanthanum from the trcCapsule into the GI tract was investigated.

Serial recordings were made in supine position taken after oral intake of 3, four-times coated enteric trcLanth.Carb. capsules of 292 mg elemental lanthanum, every 45 to 60 minutes for a total of 360 minutes. We expected all particles, visible as diffuse punctiform intraintestinal, to arrive in the colon about that period. The ULDCT scan protocol was derived by adjusting the standard CT abdomen protocol with reduced exposure parameters and the use of iterative reconstruction available on the system, Adaptive Statistical Iterative Reconstructions. We reduced the field-of-view with the exclusion of the lower abdomen or genitals to further reduce the radiation exposure. Tube voltage was reduced from 120 kV to 80 kV with a tube current of 50 mA. The data were reconstructed with 100% Adaptive Statistical Iterative Reconstructions. The effective dose of 1 ULDCT scan of the abdomen (CTDIvol = 1.4 mGy, DLP = 55 mGycm) was between 0.3 and 0.4 mSv, compared with 10.4 mSv for a standard diagnostic CT-scan (CTDIvol = 12.7 mGy and DLP = 673 mGycm). For a standard abdominal plain radiograph, the effective dose is about 0.8 mSv (2 projections). This reduction in dose caused a reduction in image quality but remained sufficient for the topographic purposes of the scan. The GI tract is divided into 6 compartments: stomach, duodenum, proximal half small intestine, distal half small intestine, right colon, and left colon. Scoring will be 0, if no lanthanum particles are present in the compartment; 1 if a complete capsule is present; 2, if large fragments of the capsule ± a minimum of punctiform fragments are present; 3, if larger and punctiform fragments are visible; 4, if mainly punctiform fragments are present in a compartment.

Furthermore, in patients with PH, CT imaging can quantify and follow-up medullary nephrocalcinosis in patients treated with trcLanth.Carb.

Laboratory Assays of Oxalate in Urine and Stability of Oxalate and Crystals in Urine

The determination of oxalate was not an easy laboratory assay.[1–3] In short, 100 µl homogenized urine or EDTA-plasma, 50 µl internal standard (500 mg/l oxalic acid C-13 (Eurisotop, Germany) in ultrapure water (Millipore, Merck, Germany), and 300 µl 1M HCl (Benelux Scientific Belgium) in butanol (Filter Service Belgium) were vortexed for 10 seconds. After incubation for 30 minutes at 65 °C (± 5 °C), samples were cooled down to 20 °C (± 5 °C) and centrifuged for 15 minutes at 10,900 rpm; 150 µl of the supernatant was then transferred into a vial and closed with a crimp cap; 10 µL was injected in the LC-system. A matrix-based control (pool) was used at the beginning of each run after the calibration curve. The analysis was performed on a Shimadzu LC system coupled with a Sciex 5500 triple quad MS (Sciex Danaher, USA). Gradient elution was performed using 1 ml of formic acid in ultrapure water (eluent A) and 1 ml of formic acid in acetonitrile (eluent B). A Luna Omega 3 µm Polar Column (Phenomenex, USA) was used for chromatographic separation. Quantification was carried out with the multiple reaction monitoring transitions of 203.2/57.0 for oxalic acid and 205.2/57.1 for the internal standard oxalic acid C13. An external quality control sample for the determination of oxalate in urine is performed 4 times a year (RfB Referenzinstitut fur Bioanalytik, Germany). This oxalate method is an in-house method based on the literature.[27,28]

The stability of oxalate under different storage conditions was evaluated using the urine of a patient with PH, urine-based quality control samples, and water. The urine was divided into 2 equal portions. One hundred ml urine was acidified with 1 ml 6M HCl and to the other 100 ml, 1 ml of water was added. Before and after acidifying, the pH of the urine was 6.66 and 2.29, respectively. The urine samples were aliquoted into 100 µl and 4 ml fractions after mixing with a magnetic stirrer enough for 1 oxalate determination and 1 analysis with the FUS-3000, respectively. Samples were kept at room temperature (20 °C–25° C), fridge temperature (2° C–8 °C) and frozen (−18 °C to −22°C) (Supplementary Text S3).

Proof-of-Concept Study Design

For the proof-of-concept study, we recruited 4 patients with clinical, biochemical, and genetic evidence of a particular type of PH (as per the Consensus Statement published in 2023),[30,31] without other major comorbidities. The patients aged > 9 years and were capable of swallowing the trcLanth.Carb. capsules. They had an estimated glomerular filtration rate > 60 ml/min per

1.73 m^2. During the control period, we collected at least 2, 24-hour urine assessments showing urine oxalate levels higher than the upper reference limit (0.51 mmol/24 h per 1.73m^2, 45 mg/24 h per 1.73 m^2).

Patients received a starting dose of trcLanth.Carb. of 1500 mg/d divided over 2 shifts during the 2 main meals. Doses were increased up to 3500 to 4000 mg/24 h per 1.73 m^2 (2336 mg of elemental lanthanum) depending on the urinary oxalate concentrations. Doses for children were calculated according to their body surface area. Capsules of 250 mg lanthanum carbonate were available.

Stimulation of hyperhydration of 2.5 to 3 l/d in adults, and 2.5 to 3 l/1.73 m^2 body surface area in children was recommended. The patients were advised not to consume vitamin C supplements and vitamin C-rich diet during the study. Crystallization inhibitors were not given during the trial period, and the intermittent intake of pyridoxine (patients 2 and 3) was stopped.

After a biological screening, the patients were seen every month during the control period, the treatment period, and after stopping the intake of the drug. End-of-treatment was decided as soon as the patient reached at least 2 successive 24-hour urine collections with oxalate concentration <0.51 mmol/l per 1.73 m^2, < 45 mg/l per 1.73 m^2.

The patients were asked to collect their 24-hour urine at least 2 times a week. In all 24-hour urine collections and in a blood sample taken during the visit, oxalate, creatinine, calcium, and phosphate were measured. Urinary oxalate was estimated as mg/l per 1.73 m^2, as mg/24 h per 1.73 m^2, and as mg oxalate/g creatine, in the 24-hour urine collections, using the age-related reference values in interpreting urinary oxalate-to-creatinine ratios.[28]

This proof-of-concept trial as well as the participation of healthy volunteers or patients with PH in the radiological investigations and in the urine sampling for crystal evaluation were approved by the institutional review board or ethical committee of the Gent University Hospital and the Antwerp University Hospital. All the patients or their legal guardians provided written informed consent. Special attention was given to the safety information of the drug in use for another indication since 25 years.[32-35]

RESULTS

Oxaluria After the Intake of Coated trcLanth.Carb. in a Normal Volunteer

Pilot experiments were performed using capsules with different coating procedures (none, 1, 2, 4, and 5 layers) in a normal volunteer. Daily 24-hour urine collections were obtained during the time of the experiment: control, during treatment 1 week, and during washout periods 3 to 5 days after treatment. In all these 24-hour urinary collections, oxalate, phosphate, calcium, and creatinine levels were determined. Determination of creatinine levels allowed to confirm the accuracy of the 24-hour collections.

Using Fosrenol (powder), no effect on oxaluria and decrease in phosphaturia was observed. Using the capsules without coating or with 1 or 2 coating layers, there was no or a negligible effect on oxaluria, and calciuria. Phosphaturia decreased (results not shown).

However, when 4-fold coated capsules were used, there was a clear effect on the oxaluria, up to more than 40% decrease in urinary oxalate compared with the control values (Figure 1). No clear effect was observed on phosphaturia and calciuria during this short clinical test (Figure 1). Three days after the end of intake, oxaluria was comparable to the control values. When using capsules with 5 layers of the coating, a comparable effect to the 4-layer coated capsules was observed on oxaluria, phosphaturia and calciuria.

Radiographical Investigations

In total we performed 7 serial ULDCT scans at 0, 45, 90, 150, 210, 270, and 360 minutes, as well as 6 X-ray AP images in 1 individual with normal renal function with a total estimated dose of 4.1 mSv. A standard diagnostic CT of the lumbar spine equals an estimated dose of 7.0 mSv. Immediately after swallowing 3 capsules (4x coated), they appeared on the first image "minute 0" unchanged in the stomach. After 45 minutes the capsules broke up into 6 larger fragments that slid into the duodenum and jejunum. Subsequently, after 90 minutes, we saw that the larger fragments moved further toward distal, with only a small amount of punctiform particles of lanthanum in the proximal half of the small intestine, on ULDCT. One hundred fifty minutes after oral ingestion, the larger capsule fragments were located approximately at the level of the distal ileum and more punctiform lanthanum particles became visible travelling distally. In the next 120 minutes, slow distal progression of the larger capsular fragments and accumulation of punctiform particles in the distal ileum was seen, indicating further release of the capsules. After 270 minutes, almost complete release in the distal portion of the ileum was seen except for 3 larger capsular fragments. On the last image after 360 minutes, all remains were in the colon and the most distal capsule remnant was located in the hepatic angle of the colon (Table 1 and Figure 2).

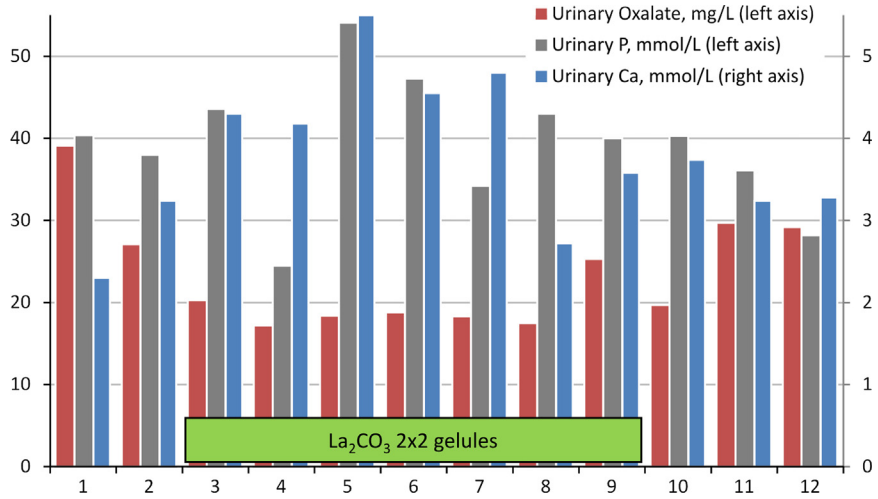

Figure 1. Effect of trcLanth.Carb. on oxaluria, phosphaturia, and calciuria in a normal volunteer. Two 4-times coated capsules of trcLanth.Carb. (500 mg) in the morning and 2 capsules in the evening, each containing 290 mg of elemental lanthanum given to an adult with normal renal function. Total daily dose: 1000 mg lanthanum. Sustained decrease of oxaluria during treatment and returning to control values 3 days after the end of treatment. Phosphaturia and calciuria remained stable.

Proof-of-Concept in Patients With PH

A summary of the most relevant results of the proof-of-concept (off-label use) of trcLanth.Carb. in 4 patients with PH types 1 and 3 is shown in Figure 3 and Table 2. The 4 patients were proposed to continue the standard-of-care regimen (stop intake of pyridoxine) that had been in place at the time of enrollment in the trial. The levels of oxaluria of 0.40 mmol or 35 mg/l per 1.73 m^2 combined with a calciuria of >4 mmol or 160 mg/l per 1.73 m^2 are considered as prone to initiate the CaOx crystal formation.[31]

Table 1. Topographical scoring of absence or presence of lanthanum over time after ingestion of 3 to 4 times trcLanth.Carb. of 250 mg elemental lanthanum in the GI tract of 3 patients with PH[a]

	Time after ingestion						
GI Location	0′	45′	90′	150′	210′	270′	360′
Stomach pt1	1	2	0	0	0	0	0
Stomach pt2	1	2	0	0	0	0	0
Stomach pt3	1	2	0	0	0	0	0
Duodenum pt1	0	2	2	0	0	0	0
Duodenum pt2	0	2	0	0	0	0	0
Duodenum pt3	0	2	0	0	0	0	0
Proximal half small intestine pt1	0	2	2	2	2	0	0
Proximal half small intestine pt2	0	2	0	0	0	0	0
Proximal half small intestine pt3	0	2	0	0	0	0	0
Distal half small intestine pt1	0	0	0	3	3	4	4
Distal half small intestine pt2	0	0	2	0	0	0	0
Distal half small intestine pt3	0	0	4	4	0	0	0
Right colon pt1	0	0	0	0	0	0	4
Right colon pt2	0	0	2	3	4	4	4
Right colon pt3	0	0	3	4	4	4	4
Left colon pt1	0	0	0	0	0	0	0
Left colon pt2	0	0	0	0	0	0	3
Left colon pt3	0	0	0	3	3	3	3

′, minutes; GI, gastrointestinal; PH, primary hyperoxaluria; Pt, patient.
[a]The GI tract is divided into 6 compartments as follows: score 0, if no lanthanum particles are present in the compartment; score 1, if a complete capsule is present; score 2, if large fragments of the capsule ± a minimum of punctiform fragments are present; score 3, if larger and punctiform fragments are visible; score 4, if mainly punctiform fragments are present in a compartment.

Elimination of Oxalate in Urine Concentrations

Absolute change in 24-hour urinary oxalate excretion (in mmol/24 h) in the 4 patients with PH from baseline to end of each treatment were as follows: 1: −2.15; 2: −0.97; 3: −0.41; 4: −1.91; mmol/24 h per 1.73 m^2 mean of −1.19 ± 0.51.

Number of patients with 24-hour urinary oxalate excretion ≥ 1.5 x upper limit of normal (0.78 mmol, 68 mg/1.73 m^2) at end of treatment: 0.

Number of patients with 24-hour urinary oxalate excretion ≥ upper limit of normal (0.51 mmol/24 h per 1.73m^2, 45 mg/24 h per 1.73 m^2) at end of treatment: 1/4.

Number of patients with oxaluria below 0.4 mmol/l per 1.73 m^2 or 36 mg/l per 1.73 m^2 is $n = 4$. Three out of four patients had calciuria below 4 mmol/l or 160 mg/l. These are concentrations considered as "non-crystal formation".[1]

The concentrations of urinary oxalate (mg/l, mmol/l per 1.73 m^2) in the 4 cases were < 45 mg/l 0.51 mmol/l per 1.73 m^2 in 26 of the 30 determinations at the end of the proof-of-concept trial, before the end of treatment.

Patient 2 had an excretion of 0.85 mmol/1.73 m^2, 74 mg/1.73 m^2 of oxalate in 24-hour collections at the end of treatment. His diuresis was 2864 ml/24 h per 1.73 m^2, meaning 0.29 mmol/l per 1.73 m^2 or 25.8 mg/l per 1.73 m^2, remaining clearly less than the critical value of crystal or small stone formation in the renal tubules or urine, demonstrating the essential information of a correct, creatinine-controlled 24-hour urine collections in patients with PH.

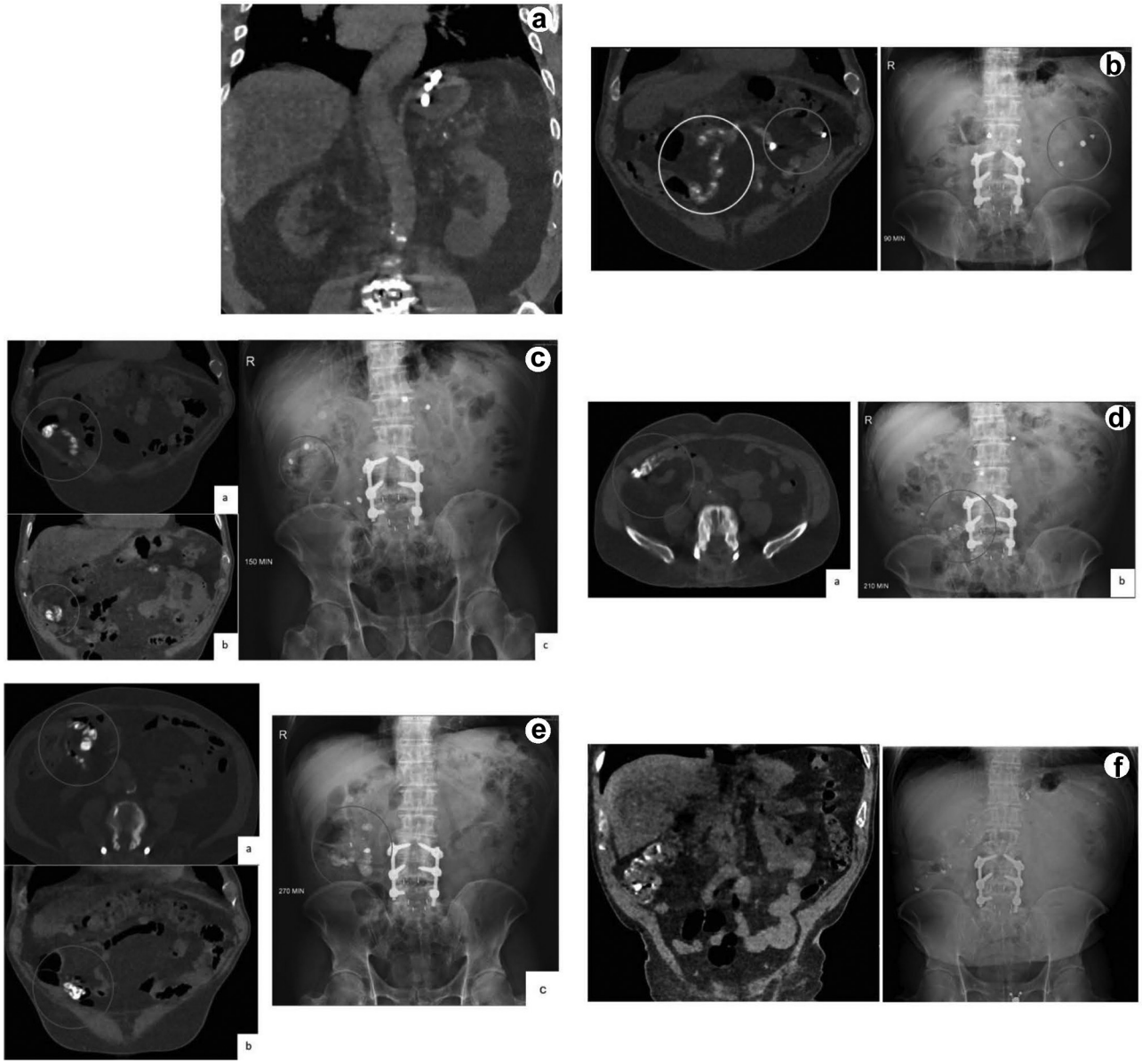

Figure 2. (a) Coronal ultra–low-dose CT (ULDCT) showing entire capsules arriving in the stomach at 0 minute. (b) Coronal ULDCT and X-ray (right) showing breaking up of the 3 capsules into larger capsular fragments in the jejunum (blue circle). Also start of release of punctiform particles seen on CT (yellow circle), but not obvious on X-ray. (c) a, b, c. Coronal ULDCT (a, b) and X–ray (c) shows the release of small particles in the distal portion of the ileum 150 minutes after ingestion of entire capsules of trcLanth.Carb. (blue and green (idem …) circles indicating the corresponding areas). (d)a, b. Coronal ULDCT (a) and X–ray (b) shows slow distal progression of the larger capsular fragments and accumulation of punctiform particles in the distal ileum (blue circle) after 210 minutes. (e) Three larger capsular fragments containing lanthanum are still seen. (f) Coronal ULDCT (left) and X-ray image (right) showing all lanthanum punctiform particles within the colon after 360 minutes. CT, computed tomography.

Patient 3, who was aged 11 years at the time of the trial, had a diagnosis of PH type 3. Correction (45×4) + $7 \div 90 + 45 = 1.38$ m^2; weight in kg = 45) of oxalate level for body surface area to 1.73 m^2, enabling interpretation of pediatric results using the adult reference range, considering values of < 0.51 mmol/24 h per 1.73 m^2 as normal.[36]

Having a 24-hour oxaluria of 0.62 mmol in the control period, after correction for her body surface $1.73 \div 1.38 = 1.25$ becomes: $0.62 \times 1.25 = 0.77$ mmol/24 h per 1.73 m^2, 66.9 mg/24 h per 1.73m^2. At the end of the treatment, she had 0.28 mmol/24 h; $0.28 \times 1.25 = 0.35$ mmol/24 h per 1.73 m^2, 30.4 mg/24 h per 1.73 m^2.

Patient 4 had problems with compliance and availability of the trcLanth.Carb. because of periods of 2 to 3 months absence from Belgium and staying with his family for 3 months in his native country explaining the long time period of his treatment.

In view of the encouraging results of the present limited study, we are preparing a randomized controlled

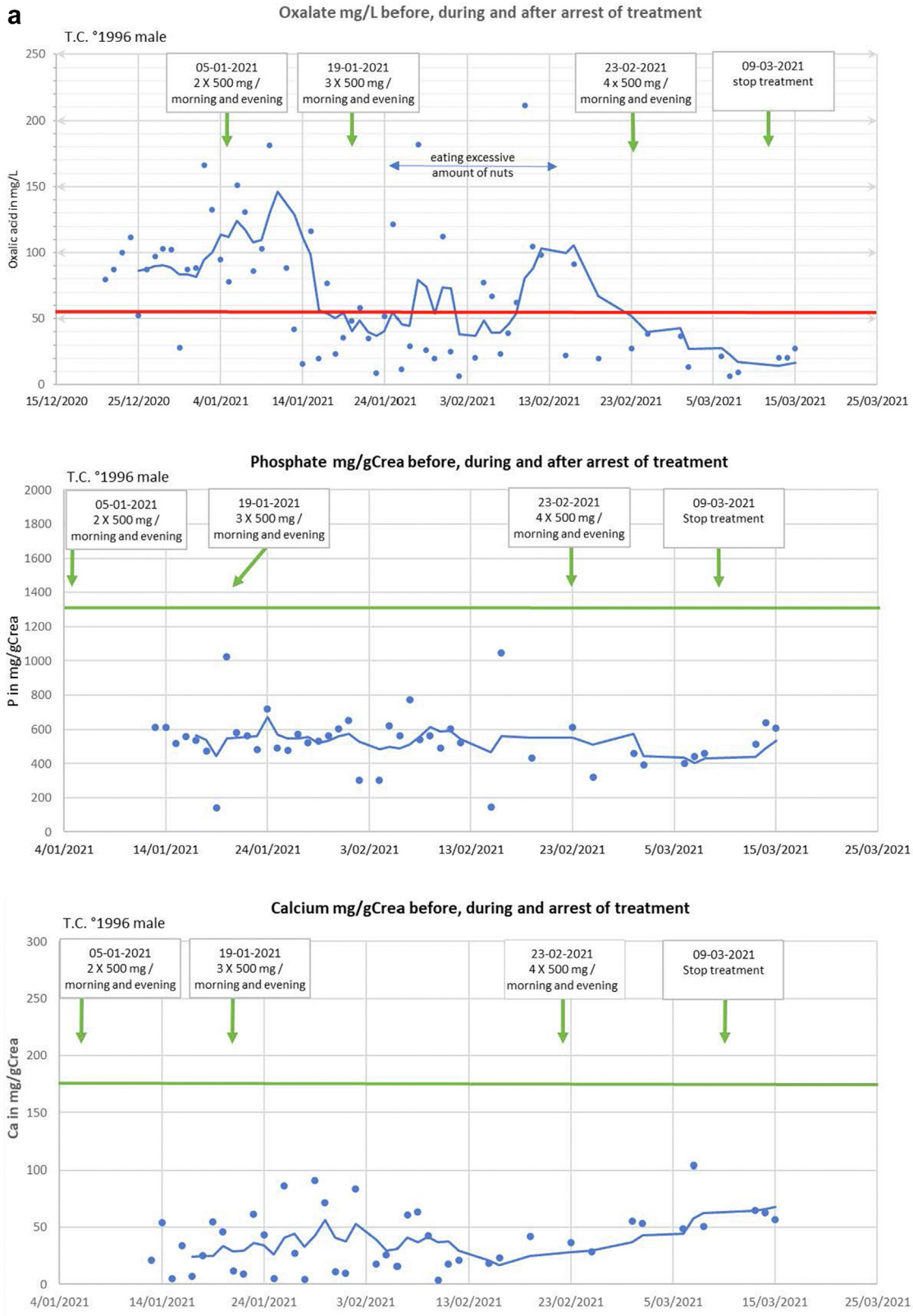

Figure 3. (a) Three pictures of patient 1. His curve of oxalate in mg/l over the duration of the treatment and 2 figures showing his phosphaturia and calciuria being stable and normal over the duration of the trcLant.Carb treatment. (Continued)

trial in Belgium, Algeria, and Morocco. Urine samples of a patient with PH and a normal volunteer were exposed to room temperature, fridge temperature (4 °C–6 °C), freeze temperature (−20 °C to −30 °C) with and without additives (HCL) (Supplementary Text S3, Supplementary Table S1, and Supplementary Figure S1).[S2,S3]

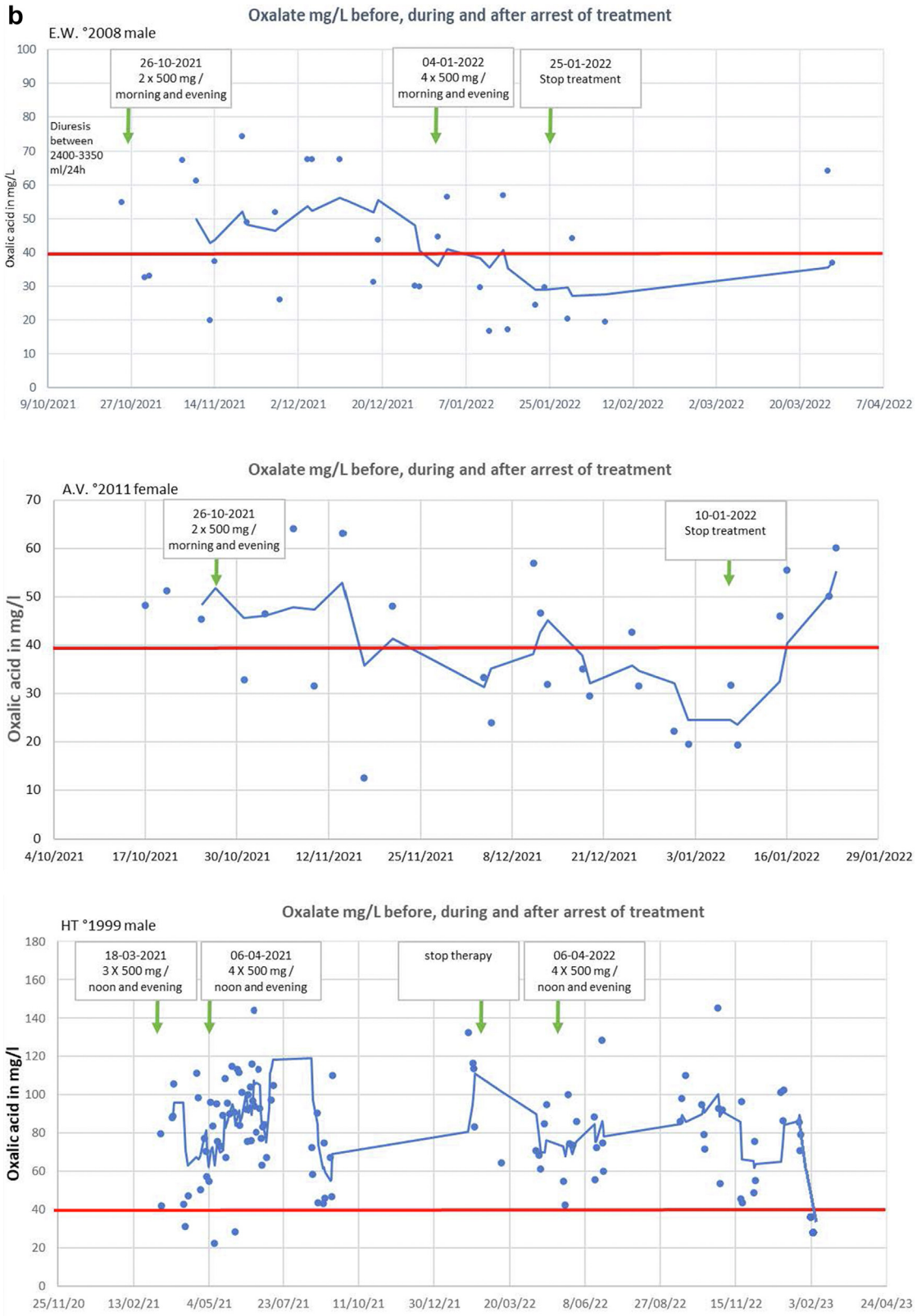

Figure 3. (Continued) (b) The 3 remaining patients: evolution over time of oxalate in mg/l over the treatment period. Their phosphaturias and calciurias are stable and normal as is in patient 1.

DISCUSSION

Lanthanum is a rare-earth trace metal and a powerful phosphate binder. Lanthanum is a trivalent metal or cation, when taken orally, binding a number of anions such as ingested phosphate and oxalate; both substances having a high comparable affinity to lanthanum. Lanthanum has been in use over the past 20 years as a phosphate binder in hyperphosphatemic

Table 2. Summary of the most relevant results of the proof-of-concept (off label use) of trcLanth.Carb. in 4 patients with PH 1 and 3

Patient number	1	2	3	4
Gender	Male	Male	Female	Male
Weight (kg)	70	53	45	73
Height (m)	1.69	1.72	1.42	1.68
Year of birth	1996	2008	2011	1999
Type of PH, genetics	1	1	3	1
Nephrolithiasis	++	++	+	+++
Medullar nephrocalcinosis	-	-	-	+
eGFR, ml/min per 1.73 m^2 (Epi)	102	109	98	74
Diuresis, l/24 h, mean ± SD	2.46 ± 0.32 ($n = 21$)	2.86 ± 0.16 ($n = 31$)	1.19 ± 0.35 ($n = 28$)	2.24 ± 0.62 ($n = 95$)
Oxaluria[a]				
. start l end R (mg/l per 1.73 m^2)	91 ($n = 9$) l 17 ($n = 9$)	54 ($n = 2$) l 26 ($n = 13$)	59 ($n = 4$) l 26 ($n = 7$)	98 ($n = 4$) l 29 ($n = 2$)
% decrease oxaluria	221 l 43	52	56	70
. start l end R (mg/24 h per 1.73 m^2)		140 l 74	67 l30	220 l 65
% decrease oxaluria	81	48	55	71
. start l end R (mg/g creatinine)	117 l 42	111 l 49	68 l 31	99 l 15
% decrease oxaluria	75	66	54	85
Duration of treatment	2.5 mo	3 mo	2 mo	1 yr 7 mo
Phosphaturia (mg/l)[b] mean ± SD	641 ± 283 stable over time	306 ± 116 stable over time	911 ± 460 stable over time	447 ± 137 stable over time
Calciuria (mg/l)[c] mean ± SD	23 ± 10 stable over time	25 ± 12 stable over time	187 ± 79 stable over time	17 ± 11 stable over time
Phosphaturia (mg/kg/d)	22.5	14.4	24.2	13.7
Calciuria (mg/kg/d)	0.80	1.10	4.51	0.53

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Epi, CKD Epidemiology Collaboration formula; PH, primary hyperoxaluria; ULN, upper limit of normal.
[a]Oxaluria normal values (ULN): <0.51 mmol/24 h per 1.73 m^2. Values expressed in mg/l per 1.73m^2 or mg/24 h per 1.73 m^2 or mg/g creatinine.[36]
[b]Phosphaturia normal value: 315 to 1200 mg/l.
[c]Calciuria normal value: < 160 mg/l, 4 mmol/l.
Numbers between brackets are the number of 24-hour urine collections (diuresis) and the number of oxaluria analyses performed.
Note the normalization of oxaluria in all patients over 2 to 2.5 months. Patient 4, with moderate CKD had to be treated for 19 months. Phosphaturia remained normal and stable during the whole treatment period; calciuria was normal and remained stable over the whole treatment period in the 4 patients with PH. All patients except patient 3 had 24-hour urine of more than 2 L.
Patient 3 had slightly increased calciuria classically observed in patients with PH type 3. All 4 patients had an oxaluria < 0.4 mmol/l or 36 mg/l and 3/4 a calciuria < 4 mmol/l or 160 mg/l: noncrystal forming concentrations.[1]

dialysis patients in many countries, without appearance of serious side effects.[30,31] Dialysis patients with almost no renal function accumulate phosphate, the kidney being the organ playing the dominant role in the metabolism of phosphate. There is no accumulation of Lanthanum in dialysis patients because its absorption in the GI is very low (0.002%), indicated by plasma levels after some years in dialysis patients, in the ng/l range.[32]

In contrast, in patients with normal or slightly decreased renal function (estimated glomerular filtration rate ≥ 45 ml/min per 1.73 m^2), phosphate depletion occurs after some time when powerful phosphate binders (aluminum hydroxide, lanthanum carbonate) are used.[9–14] This is expressed by a substantial decrease of the phosphaturia,[10,13] with phosphatemia remaining normal, a reflection of the mobilization of phosphate from bone (demineralization, osteomalacia) in order to maintain a stable serum phosphate level. Furthermore, tibia sections of rats treated with lanthanum show cortical bone loss and osteomalacia in the presence of active healthy osteoblasts.[10–14] In other words, lanthanum is not directly toxic for the osteoblasts; however, by depleting the bone from phosphate, it may induce a dangerous, reversible, loss of phosphate/osteomalacia.

In addition, because the concentration of phosphate is at least 10 times higher compared with oxalate in daily ingested food, Lanth.Carb. (Fosrenol) administered orally will mainly chelate phosphate starting in the stomach, duodenum, and jejunum decreasing in the last part of the GI tract.

Reports have shown that the GI absorption of phosphate in humans takes place mainly at the level of the proximal intestine (duodenum to jejunum) and less in the colon, whereas oxalate is reabsorbed and secreted substantially[19,20] in the ileum and proximal colon. The colon is the site of, and required for, optimal oxalate absorption in enteric hyperoxaluria,[37,38] a clinical situation associated with an increased free oxalate concentration in the gut. Furthermore, the distal part of the small intestine and the proximal colon are the places where most of oxalate[24,25] secretion (SLC 26A6–mediated) occurs in humans,[18] secretion which increases substantially in CKD,[22–26] considered as an adaptive mechanism. Indeed, in case of CKD, percent excretion of 14C-oxalate via the gut increased, showing a significant inverse correlation with the creatinine clearance.[22] The basal absorption (12.8 ± 2.22 pmol) of oxalate across the colon was changed to secretion (−14.96 ± 2.57 pmol/CM2/h) in animals with chronic renal failure.[25]

The setting of the late small intestine and colon where oxalate is degraded by *Oxalobacter sp*. bacteria reducing urinary[21] oxalate excretion creates a more pronounced oxalate gradient (serum − colon lumen), thus promoting enteric oxalate secretion. Indeed, SLC26A1 is expressed on the basolateral membrane, mediating basolateral oxalate uptake, which together with apical oxalate efflux via SLC26A, facilitate intestinal oxalate secretion into the colon.[23,24] TrcLanth.-Carb. can also be considered as a "vacuum cleaner" of oxalate (formation of an inert complex oxalate-lanthanum) in the distal GI tract containing unchelated lanthanum and thus stimulating the secretion of oxalate from the central (serum) compartment to the ileum and colon by the SLC26A6 transporters.

In patient 1, it was demonstrated that the contribution of the serum to colon secretion (SLC26A transporters) of oxalate is many times (5×) the chelated amount of the ingested oxalate (Supplementary Text S4; Supplementary Figure S2).

These elegant observations are highly relevant for patients with PH with end-stage renal failure or on dialysis and exposed to a progressive oxalate loading of tissues or organs named oxalosis. The increased capacity of the SLC26A6 transporters mediated secretion of oxalate in the distal part of the GI tract in CKD, *a fortiori* in dialyzed patients with PH, opens perspectives. Indeed, the combination of intense dialysis (mean dialysis extraction of 175 mg/session),[39] combined with suppression of oxalate synthesis by RNA inhibitor treatment and trcLanth.Carb. (chelation and secretion of oxalate) is currently under investigation. These 3 independent, different ways of removing oxalate from the body may result in a cumulative effectiveness resulting in plasma oxalate levels permitting a renal transplantation without oxalate deposition in the kidney allograft. Three recent published studies produced the first promising results in that field using intense dialysis combined with RNA inhibitor (lumasiran).[40–42]

ULDCT scanning seems very helpful in identifying the exact location of the lanthanum capsular fragments and punctiform particles, whereas this topography is not always so easily done in standard X-ray imaging because of 2D projection. In view of the lower radiation dose and the higher topographic features, ULDCT is more informative than standard X-ray imaging.

In contrast, overview of distribution of the lanthanum particles is easier with X-ray compared to CT, the identification of individual punctiform particles is superior using X-ray, secondary to the higher spatial resolution inherent to the technique. The experiment was conducted a second time in the same volunteer after 6 months. In the first experiment, we saw a similar progression of the lanthanum release with topographic release of the particles, mainly in the distal portion of the ileum and colon. There was a difference in timing of this release where larger particles remained more intact with a time difference of 30 to 60 minutes. This illustrates some variability within one person, which is to be expected because bowel movements and content are not always identical in time. Given that we want the most representative data in normal daily life, we did not give any dietary instructions to our volunteer.

The main release of lanthanum particles in the distal portion of the ileum and colon is also supported by the normal and stable values of phosphaturia observed in the 4 patients with PH who received these capsules for 2.5 months to 17 months (Table 2).

One important conclusion about the confrontation of the different ways of presentations of the urinary oxalate values in patients with PH is that the most relevant one is the concentration of urinary oxalate in mg/l associated with the controlled information of the 24-hour urine collection (creatinine determination), avoiding the frequently observed errors from sloppy collections.[43] The 24-hour value of oxalate in urine loses part of its impact in the absence of the data obtained from a correct 24-hour collection of urine by the patient with PH. Expressing the oxalate concentration in mg/l is the most relevant parameter in the evaluation of the yes or no modus of crystal formation (< 0.4 mmol/l per 1.73 m^2, 36/1.73 m^2 mg/l per 1.73 m^2 of oxalate associated with 4 mmol/l per 1.73 m^2 160 mg/l per 1.73 m^2 of the calciuria)[2] in the urine of a particular patient with PH. In case the oxalate production (liver) + absorption (GI tract) results in an urine oxalate concentration of 80 mg/24 h per 1.73 m^2 in a particular patient with PH, this situation remains innocent as long this patient urinates 2.5 l urine/24 h and consequently has oxalate concentration of 32 mg/l per 1.73 m^2, 0.34 mmol/l per 1.73m^2, which is below the critical level of crystal formation in urine. The patients of the presented proof-of-concept are in a condition (Supplementary Text S5) where CaOx crystal formation in the urine was occurring (levels >450 crystals/μL, mainly whewellite type) as demonstrated in 3 of the 4 cases with PH using FUS 3000 analysis of fresh urine of the control period. At the end of the treatment, no crystals or low levels (< 150 crystals/μl) were observed (Supplementary Figure S3 and Supplementary Table S2).

Diagnosis of PH is often delayed or missed owing to its rarity, variable clinical expression, and other diagnostic challenges, such as quality of urinary and plasma oxalate determinations (as explained in the Methods section: Laboratory Assays of Oxalate in Urine and Stability of Oxalate and Srystals in Urine). Among

the recent recommendations, published by representatives of OxalEurope, ESPN, ERKNet, and ERA,[31] the prominent ones in order to obtain a diagnosis of PH are: 2 positive collections of 24-hour urine (concentration of oxalate $\geq$ 0.51 mmol/24 h per 1.73 m^2 or 46 mg/24 h per 1.73 m^2urine), using age-related values in interpreting urinary oxalate-to-creatinine ratio, genetic testing[31,36] for the different types of PH, and CaOx crystals in volume or number (>200 pure whewellite crystals/µl urine).

In a series of publications of studies, M. Daudon and his coworkers have demonstrated the value of crystalluria analysis, and that particularly measuring crystal volume and morphology (identification) are helpful in evaluating the efficacy of a treatment, optimizing the medical management and an early diagnosis of PH.[44-46] The determination of crystalluria is of help in the follow-up of patients with severe forms of nephrolithiasis, because it reflects the activity of stone disease, posttransplantation monitoring (CaOx deposition) in patients with PH 1, and the response to therapeutic measures in PH.[46] The concentration of urinary oxalate determines crystal formation.[44,45] The goal after transplantation is to achieve negative crystalluria or an oxalate crystal volume of <100 $\mu m^3/mm^3$ by means of hydration and other symptomatic measures.+

Nevertheless, 2 recent interesting reviews or guidelines[31,47] described their positive critical position and "weak recommendation" concerning this crystalluria analysis.

The Consensus Group agreed that research has shown that evaluation of urinary crystals could be very valuable; however, the group recognizes that the existing methods for assessment of crystalluria do not allow this to be part of stone treatment in many places.[47] They also recognize that research into new methods (Supplementary Text S5), standardization of reporting criteria, and further research into how to apply test results for patient diagnosis and treatment will all be important for making crystalluria determination more widespread in the treatment of stone diseases.

CONCLUSION

We developed a performant oxalate chelator, trcLanth.Carb. released in the distal part of the GI tract, as proven by the normalized oxalurias and normal unchanged stable phosphaturia in 4 patients with PH (types 1 and 3) at the end of the treatment. The pharmacology of Lanth.Carb. was changed by creating a delivery of lanthanum in the distal part (ileum and colon) of the GI tract. A rather powerful phosphate binder becomes an efficient oxalate chelator, not interfering with the GI phosphate metabolism. A new, efficient, nontoxic, free of serious side effects, cheap, and drug trcLanth.Carb., may deserve a place in the armamentarium of the prevention and treatment of PH of any type and in any part of the world, partly filling the gap between the developed and developing world, provided the planned randomized controlled multicenter trial confirms the positive results of the proof-of-concept.

DISCLOSURE

All the authors declared no conflicting interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Text S1. Literature study: Prevalence estimation of primary hyperoxaluria in Europe.

Text S2. Exclusion criteria.

Text S3. Stability of urinary oxalate concentrations, number and diameter of CaOx crystals under different storage conditions in time.

Text S4. Relative contribution of 2 distal gastrointestinal oxalate eliminating pathways in humans.

Text 5. Crystalluria.

Figure S1. Stability of oxalate and CaOx-crystals in urine of a P.H. patient kept in fridge without additives.

Figure S2. P.H. patient nr. 1 (male, °1996): treatment of 2.5 months with sdcLanth.Carb. develops a decrease of oxaluria (mg/24h/1.73m^2) of 81% compared with the control values.

Figure S3. FUS 3000 urine analyser (DIRUI)I Identification of number, shape, and size of CaOx. crystals in urine samples.

Table S1. Stability over time of the determination of oxalate and CaOx-crystals in urine using different methods of storage.

Table S2. Crystalluria in normal individuals and in 3 patients with primary hyperoxaluria.

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