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Treatment of primary hyperoxaluria type 1

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ABSTRACT

Supportive treatment for primary hyperoxaluria type 1 (PH1) focuses on high fluid intake and crystallization inhibitors. A subset of patients with specific PH1 genotypes (c.508G>A and c.454T>A) will respond to pyridoxine, defined as a >30% reduction in urinary oxalate excretion. Response to pyridoxine is variable and in some patients, urinary oxalate may normalize. The first focused treatment for PH1 using an RNA interference agent to reduce urinary oxalate was approved in 2020, and such therapies may significantly alter treatment approaches and long-term outcomes in PH1. Currently PH1 often presents with kidney function impairment and frequently results in end-stage kidney disease (ESKD). With kidney dysfunction, urinary oxalate clearance decreases and multisystem deposition of oxalate (oxalosis) occurs, commonly in bones, eyes, heart and skin. Once plasma oxalate levels exceed 30 µmol/L, aggressive haemodialysis is indicated to prevent oxalosis, even if the glomerular filtration rate (GFR) remains better than for typical dialysis initiation. Peritoneal dialysis alone does not achieve the needed oxalate clearance. Dialysis is a bridge to future transplantation. Liver transplantation restores hepatic alanine-glyoxylate transaminase enzyme activity, allowing glyoxylate detoxification and preventing further oxalosis. The native liver must be removed as part of this process to avoid ongoing pathologic oxalate production. The timing and type of liver transplantation are dependent on pyridoxine sensitivity, age, weight, residual GFR and evidence of systemic oxalate deposition in extrarenal organs. Liver transplant can be isolated or combined with kidney transplantation in a sequential or simultaneous fashion. Isolated kidney transplantation is generally reserved for pyridoxine-sensitive patients only. Although liver transplantation is curative for PH1 and kidney transplantation treats ESKD, ensuing necessary immunosuppression and potential allograft dysfunction impart significant long-term risks.

Keywords: dialysis, infantile PH1, kidney failure, lumasiran, nedosiran, oxalosis, PH1, primary hyperoxaluria, RNAi, transplantation

Until 2020, treatment to prevent nephrolithiasis/nephrocalcinosis associated with PH1 involved only general common supportive stone prevention measures. Only a small subset of patients with PH1 respond to pyridoxine as a specific treatment, with a variable reduction in urinary oxalate (UOx). Alternative treatment strategies include pre-emptive isolated liver transplantation (ILT) in patients unresponsive to pyridoxine with preserved kidney function. Patients with end-stage kidney disease (ESKD) may require liver–kidney transplantation, usually with a period of intensive combined haemodialysis (HD) and peritoneal dialysis (PD). A small subset of patients with pyridoxine sensitivity and ESKD may be amenable to isolated kidney transplantation (KT). In 2020, the first focused treatment for PH1 using an RNA interference (RNAi) agent to reduce UOx was approved.

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MEDICAL THERAPY

Supportive treatment for PH1 includes hyperhydration and crystallization inhibitors. These manoeuvres should be initiated pending genetic confirmation of disease in any patient with high UOx in whom PH1 is suspected and who does not have risk factors for enteric hyperoxaluria. Hyperhydration should be prescribed at 2–3 L/1.73 m^2/day. Enteral tubes may be indicated in infants to achieve prescribed fluid goals [1–4].

Citrate complexes with urinary calcium and reduces urine crystallization by inhibiting crystal growth of calcium phosphate and calcium oxalate. Potassium citrate/potassium bicarbonate can be used empirically for low urinary pH or citrate content. Where glomerular filtration rate (GFR) is reduced and there is a risk of hyperkalemia, sodium citrate should be used [1–4].

The main source of oxalate in PH1 is endogenous overproduction by the hepatocyte. Hence dietary restriction has minimal impact. Nevertheless, some experts recommend avoiding high intake of oxalate-containing foods [3, 4]. Excess vitamin C supplementation should be avoided since its metabolism can also result in additional oxalate production [4].

Pyridoxine is a cofactor for alanine-glyoxylate transaminase (AGT), a pyridoxal phosphate-dependent enzyme. Pyridoxine increases the activity of mistargeted AGT and decreases oxalate production in specific variants of *AGXT* (c.508G>A and c.454T>A) [1–4]. Pending genetic confirmation of PH1, pyridoxine should be prescribed for all patients for whom the diagnosis is under consideration. Initial pyridoxine dose is 5 mg/kg/day with a maximum of 20 mg/kg/day [1, 2]. UOx values should be monitored after initiation of pyridoxine to assess response. Responsiveness to pyridoxine is defined as a >30% relative decrease in UOx from baseline within 6 months of pyridoxine initiation [1]. Negative genetic testing for PH1 or pyridoxine insensitivity are indications to stop supplementation [4]. About 30% of patients with PH1 have variants that confer pyridoxine responsiveness [5], with some showing complete normalization of UOx. As GFR decreases, response to pyridoxine by assessment of UOx is more difficult and a pyridoxine trial should continue until genetic testing results return.

A new RNAi therapy for PH1, lumasiran, was recently approved by the US Food and Drug Administration, the European Medicines Agency (EMA) and the Medicine and Healthcare Products Regulatory Agency (MHRA). Lumasiran is administered via a subcutaneous injection given monthly for the first 4 months and then every 3 months thereafter. By inhibiting glycolate oxidase, lumasiran reduces the production of glyoxylate and pathological oxalate [6].

Data from a double-blind, randomized controlled study of lumasiran showed that the majority of patients had normal or near-normal UOx levels after 6 months of treatment without serious drug-related adverse events [7]. The mean maximal reduction in 24-hour UOx from baseline after 6 months was 76% (range 35.8–93.6). At Month 6, 84% of patients receiving lumasiran had 24-hour UOx levels no higher than 1.5 times the upper limit of normal and 52% had levels equal to or less than the upper limit of normal.

Another RNAi therapy, nedosiran, inhibits the hepatic lactate dehydrogenase A (LDHA) pathway and also decreases oxalate production. Clinical trials using nedosiran are ongoing [8]. Early results from an open-label rollover extension trial showed normalization or near normalization of UOx in six of seven patients who had received more than 3 months of nedosiran. No drug-related adverse events were reported.

Utilizing RNAi therapy alone or together with KT as an alternative to CLKT is appealing and may be possible once longer-term efficacy and safety data are available.

RNAi therapy may not be appropriate for some cases, such as those with pyridoxine responsiveness. Decisions about initiating RNAi should involve the patient, family and medical teams, taking into account the current unknown long-term risks.

Cost or availability may limit the access to RNAi worldwide, necessitating the use of alternative agents such as stiripentol, an antiepileptic drug that is hypothesized to reduce oxalate production in the liver. Evidence for its ability to reduce UOx is conflicting [9–11]; however, a Phase II clinical trial in primary hyperoxaluria (PH) is currently under way. Oxalobacter formigenes (Oxabact), an anaerobic gut bacterium that avidly metabolizes oxalate, has also been investigated for therapeutic use in PH1. Phase II trials have shown improvement in plasma oxalate (POx) levels and clinical status in PH1 with ESKD [12]. However, the same reduction was not seen for UOx [13].

DIALYSIS

Kidney failure (KF) is a common and often presenting feature of PH1 [14, 15]. With advancing chronic kidney disease (CKD), urinary clearance of oxalate decreases and POx levels rise. Calcium oxalate supersaturation (β_{CaOx}) is reached when POx levels exceed 30–45 µmol/L; thereafter, significant systemic oxalate deposition occurs, resulting in oxalosis [16, 17]. Dialysis should commence at this point to maintain POx at levels less than the β_{CaOx}, even if the GFR exceeds levels for typical dialysis initiation [4].

Dialysis is most often used as a bridge to liver–kidney transplantation. Furthermore, it may be required post-operatively to protect the newly transplanted kidney from systemic stores that can cause hyperoxaluria, nephrolithiasis and nephrocalcinosis.

Endogenous oxalate generation often exceeds rates of removal using conventional dialysis strategies (4–7 versus 1–4 mmol/1.73 m^2/day) [16, 18]. The lower clearance of POx with PD versus HD (7.14 versus 115.6 mL/min/1.73 m^2) necessitates the use of the latter as a primary dialysis modality. Many individuals with PH1 require prolonged HD sessions five to six times per week, sometimes in combination with PD [19–21]. Nevertheless, achieving time-averaged oxalate levels <50 µmol/L using dialysis alone is very difficult [22].

Progressive systemic oxalate accumulation occurs the longer an individual remains on chronic dialysis. Mineral and bone disease can be profound [16]. Prolonged periods on dialysis carry an inherent increased risk of line sepsis, access difficulties, cardiovascular complications, psychosocial burden for the patient and the wider family, as well as death [23]. These issues require discussion as part of pretreatment counselling.

TRANSPLANTATION

Isolated liver transplantation

Liver transplantation can restore hepatic AGT activity, allowing glyoxylate detoxification and preventing further oxalosis. The native liver must be removed as part of this process to avoid continuous production of pathologic oxalate [24]. The timing and type of liver transplantation are dependent on pyridoxine sensitivity, age, weight, residual GFR and evidence of systemic oxalate deposition in extrarenal organs [4, 24].

Pre-emptive ILT may be possible in selected patients with a GFR >60 mL/min/1.73 m^2 [4]. Underpinning this

approach is the hope that impeding ongoing hyperoxaluria could halt the progression of kidney disease, which is seen in at least 70% of PH1 patients over time [25]. Following ILT, it is vital to monitor the GFR and consider including POx. A decrease in GFR below 45 mL/min/1.73 m^2 results in a dramatic decrease in oxalate clearance. Patients who are mobilizing systemic oxalate burden after ILT risk a more rapid loss of native kidney function from oxalate-mediated injury. Thus a pre-emptive KT may be beneficial and could be considered at a higher GFR than typical kidney replacement therapy.

Timing of pre-emptive ILT is difficult, given the lack of genotype–phenotype correlation to inform CKD progression as well as the unpredictable clinical course and tempo of GFR decline with CKD. Furthermore, ILT itself is associated with significant risks, including a 10–15% peri operative mortality rate, numerous potential medical complications and chronic immunosuppression exposure, often including agents like calcineurin inhibitors, which may themselves be nephrotoxic and augment the decline in native GFR over time [26]. Accordingly, a consensus guideline has refrained from recommending ILT as a preferred therapeutic option [4].

CLKT

Approaches to dual organ transplantation have included sequential and simultaneous liver–kidney transplantation, which have comparable outcomes [23].

A sequential procedure involves hepatic transplantation with ongoing dialysis. This may be preferable for living donation scenarios and when the patient has severe systemic oxalosis requiring a period of further dialysis to attenuate the oxalate burden prior to KT.

Simultaneous liver–kidney transplantation typically utilizes organs from the same donor. Removal of the native liver and good transplant function halt pathologic production of oxalate. POx levels can continue to be elevated, however, secondary to extensive pretransplant systemic oxalate deposition and post-transplant mobilization from tissue stores. Intensive dialysis at this point facilitates oxalate clearance and reduces the risk of deposition in the newly transplanted kidney. Certainly, any patient with concern for acute tubular necrosis or delayed graft function after a combined organ transplant needs dialysis [27]. Once the function of the transplanted kidney improves and lower POx levels are achieved, UOx can remain elevated for many years due to the slow resolubilization of systemic calcium oxalate. The supportive measures described above are essential to protect the transplanted kidney from further calcium oxalate damage through stones or nephrocalcinosis [28]. Complete clearance of tissue oxalate stores often requires several months to years following successful liver transplantation and cessation of pathologic oxalate production [21].

Isolated KT

Isolated KT is reserved for patients with significant pyridoxine sensitivity. Outcomes are comparable to CLKT [18, 28, 29, 30]. Isolated KT without the correction of the accompanying hepatic metabolic defect results in recurrence of oxalosis and increased rates of graft loss in patients with pyridoxine-insensitive PH1 [29].

Monitoring

Individuals with PH1 require lifelong surveillance [2, 4]. Young children with symptomatic or newly diagnosed disease and those on RNAi therapy require closer monitoring [4, 31]. UOx is the marker used as a surrogate to assess PH1 treatment efficacy in CKD Stages 1–3a [7, 32]. POx is thought to be a better surrogate for the risk of systemic oxalosis in CKD Stages 3–5b [32]. In addition, monitoring in these patients should include 24-hour urine collections to assess supersaturation for calcium oxalate, imaging of the kidneys and urinary tract and periodic assessment of kidney function, generally by serum creatinine measurement. If available, monitoring crystalluria, especially after transplantation, may be valuable [30]. There is a lack of robust evidence underlying many contemporary therapeutic targets for PH1, especially optimal UOx values [32].

Infantile PH

Infantile oxalosis is the most severe form of PH1, with more than half of those affected presenting after having already progressed to ESKD [14, 15]. Hence aggressive management is warranted to preserve any kidney function that still exists and to prevent oxalate deposition as well as multi-organ failure early in life. In addition to conservative measures such as hyperhydration and the use of crystal inhibitors, a trial of pyridoxine should be initiated with consideration of RNAi therapies, if available.

Historically, despite impeccable supportive care, infantile PH1 inevitably progresses to eventual ESKD. These young patients make up almost 40% of the children with PH requiring dialysis [23]. Starting dialysis not only facilitates oxalate clearance but also allows optimization of nutrition to improve growth [19, 33].

In these young children, skeletal oxalate deposition exacerbates the typical osteodystrophy that accompanies ESKD, resulting in a heightened risk of poor bone health [19, 23, 33]. Careful clinical management of bone health is vital, especially during periods of expected rapid growth such as the first 2 years of life [34]. Tracking calcium, phosphorus, vitamin D and parathyroid hormone levels allows appropriate alterations to therapies aimed at optimizing bone mineral metabolism. For example, in contradistinction to typical ESKD management, in small children with PH1 undergoing intensive dialysis, phosphate supplementation may frequently be required rather than phosphate binders.

Intensive dialysis regimens are especially complicated to maintain over time in very young children with PH1, and there needs to be great vigilance for dialysis-associated infections [20, 23, 33]. Infant survival on dialysis is lower in those affected with PH1 [23]. Such intense chronic medical therapy is also a source of profound stress for families, especially when there are concomitant financial, medical or psychosocial issues affecting primary caregivers [20].

CLKT is curative in terms of eliminating overproduction of endogenous oxalate, and timing depends on the child's size, overall health, systemic oxalate burden and potential confounding medical conditions unrelated to ESKD or PH1. Most transplant centres opt to wait until a child weights 10 kg before undergoing CLKT, although successful outcomes below this weight have been reported. Individual patient and family circumstances, medical resources and expertise should ultimately underlie a decision to go forward with transplantation [35]. Additionally, the role of CLKT in treating PH1 may change substantially in the near future with the introduction of therapies such as RNAi agents, which may effectively eliminate the overproduction of oxalate.

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CONFLICT OF INTEREST STATEMENT

A.G. is a member of the Hyperoxaluria Rare Disease Collaborative Network and has been a senior principal investigator for the Alnylam and Dicerna clinical trials. M.S. has sat on advisory boards for Alnylam and Orfan Biotech and on a drug safety monitoring board for Dicerna as part of the Nedosiran trial. M.S. reports receiving funding from Alnylam for delivering educational presentations. M.B. has sat on scientific advisory boards for Alnylam and Dicerna and the Oxalosis/Hyperoxaluria Foundation. M.B. reports receiving consulting fees from Alnylam, Dicerna, Chinook and Orfan Biotech. M.B. has been a principal investigator for the Alnylam and Dicerna clinical trials.

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