Transplantation for Primary Hyperoxaluria Type 1: Designing New Strategies in the Era of Promising Therapeutic Perspectives

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Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disease caused by the functional defect of alanine-glyoxylate aminotransferase (AGT), a liver-specific peroxisomal enzyme that catalyzes the transamination of glyoxylate to glycine. The deficiency results in the accumulation of glyoxylate and excessive production of both oxalate and glycolate (Figure 1).1 More than 190 mutations have been described in the AGT gene, which is located on chromosome 1, coding for a protein of 180 amino acids. The most common mutations are missense mutations, with a prevalence of 60% in PH1 patients.1

PHYSIOPATHOLOGY OF PH1

PH1 is an autosomal recessive disorder caused by the functional defect of alanine-glyoxylate aminotransferase (AGT), a liver-specific peroxisomal enzyme that catalyzes the transamination of glyoxylate to glycine. The deficiency results in the accumulation of glyoxylate and excessive production of both oxalate and glycolate (Figure 1).1 More than 190 mutations have been described in the AGT gene, which is located on chromosome 1, coding for a protein of 180 amino acids. The most common mutations are missense mutations, with a prevalence of 60% in PH1 patients.1

Because PH1 is caused by a liver-specific enzyme deficiency, current transplant strategies to treat ESRD include liver–kidney transplantation, combined or sequential (liver first and then kidney). However, liver transplantation is associated with morbidity and mortality. Fortunately, a therapeutic revolution for PH1 patients is looming. Indeed, many innovative drugs are currently tested to treat the metabolic defect and could avoid liver transplantation. Undoubtedly, these promising drugs will modify our approach in the management of PH1 patients with ESRD. Here we review the current knowledge on this subject and discuss views on the future of kidney transplant management in PH1 patients.
been described so far, with limited genotype–phenotype correlation.\(^1,4\)

Oxalate in the form of calcium salt is highly insoluble and is primarily excreted by the kidneys. At an early stage, PH1 often presents with recurrent kidney stones and nephrocalcinosis, which lead to progressive decline in kidney function. Subsequently, when glomerular filtration rate (GFR) drops to 30 to 45 ml/min per 1.73 m\(^2\) of body surface area (BSA), the kidney is no longer able to efficiently excrete the oxalate load it receives.\(^1\) Thereafter, plasma oxalate (POx) increases and rapidly exceeds saturation.\(^5\) This results in systemic oxalosis with oxalate deposition predominantly in bone, kidneys, skin, retina, myocardium, vessel walls, and the central nervous system.\(^1\) This systemic storage increases as the kidney function declines. If not managed properly or ignored before kidney transplantation, this systemic oxalate storage precipitates in the renal graft (Figure 2) and can lead to early allograft dysfunction or loss.

**CURRENT MANAGEMENT AND TRANSPLANT STRATEGIES FOR PH1 PATIENTS**

Conservative measures are limited and should be applied as soon as the disease is diagnosed. These measure include massive fluid intake (>2–3 L/m\(^2\) BSA per day or through tube or gastrostomy feeding in infants), calcium oxalate crystallization inhibitors (oral potassium citrate and magnesium citrate or sodium citrate in case of impaired renal function to maintain urine pH above 7), and pyridoxine (starting dose of 5 mg/kg per day that may be progressively increased up to 20 mg/kg per day).\(^1,2\) For pyridoxine (vitamin B6), an excellent (inexpensive) chaperone molecule acting on protein stability, catalytic activity, and peroxisomal import of AGT,\(^6\) there is a strong genotype–phenotype correlation in responsiveness, which mainly occurs in patients with the Gly170Arg and Phe152Ile mutations.\(^7\)

When estimated GFR (eGFR) declines under 30 ml/min per 1.73 m\(^2\) BSA, dual liver–kidney transplantation is currently proposed\(^1,8,9\) because oxalate retention increases at this stage of renal dysfunction, making the evolution to ESRD nearly unavoidable.\(^1\) In chronic kidney disease (CKD) stage 4, early combined liver–kidney transplantation is preferred when systemic storage is assumed to be quite limited (early after a patient’s eGFR declines to below 30 ml/min per 1.73 m\(^2\) BSA). Several registry studies have assessed relatively good kidney outcomes of PH1 with ESRD using this strategy. Bergstralh \textit{et al.}\(^10\) published US Renal Data System data showing 3- and 5-year death-

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**Figure 1.** Glyoxylate metabolism in the hepatocyte in primary hyperoxaluria type 1 (PH1). In the peroxisome of normal hepatocyte, glycolate oxidase (GO) catalyzes the conversion of glycolate to glyoxylate. Then, alanine-glyoxylate aminotransferase (AGT) catalyzes the conversion of glyoxylate and alanine to glycine and pyruvate and of serine to hydroxypyruvate. In PH1, glyoxylate accumulates as a result of AGT deficiency and is converted to oxalate by hepatic lactate dehydrogenase (LDH) and GO and to glycolate by glyoxylate reductase-hydroxypyruvate reductase (GRHPR). Oxalate and glycolate are finally eliminated from the body by the kidneys. RNA interference (RNAi) drugs targeting hepatic GO and LDH and stiripentol targeting hepatic LDH are currently being tested in phase II and III clinical trials as potential therapies for PH1.
censored graft survivals after combined liver–kidney transplantation of 95% and 78%, respectively. Har-ambat et al.11 published a European experience in PH1 children that demonstrated 1-, 3- and 5-year kidney graft survivals after combined liver–kidney transplantation of 82%, 79%, and 76%, respectively. In addition, Compagnon et al.12 published a French experience showing a 10-year kidney graft survival of 87%.

In CKD stage 5 or chronic dialysis, when systemic oxalosis is more intense, sequential transplantation can be another option: first the liver followed by hemodi-a lysis to decrease systemic oxalate storage and then the kidney.1,8 This in theory should limit the precipitation of oxalate in the kidney allograft. However, no clear benefit from this strategy has been reported, and choosing between combined and sequential liver–kidney transplantation remains controversial.

LIMITATIONS OF CURRENT STRATEGIES

The main issue is the need for liver transplantation, which until now was the only way to cure the liver metabolic defect. Liver transplantation is associated with many hurdles. The first is the worldwide organ shortage, which delays access to transplantation. As discussed above, this delay is particularly critical in the field of PH1 because systemic storage increases with declining GFR as long as the metabolic defect is not cleared. Second, morbidity and mortality of liver transplantation should not be minimized. Jamieson and the European PHI Transplantation Study Group13 published a European PH1 transplant registry experience from 1984 to 2004. One hundred twenty-seven liver transplants were performed in 117 patients with a mean age of 16.5 years, including 99 combined liver–kidney transplantations and 6 sequential liver–kidney transplantations. One-, 5-, and 10-year patient survival rates were only 86%, 80%, and 69%, respectively. In our opinion, although liver transplantation was ethically justified, these results are clearly not optimal in such a young population.

NEW THERAPEUTIC APPROACHES FROM ONGOING STUDIES

Several promising therapeutic agents are currently under investigation.14 The new therapeutic approaches most advanced in clinical development are reviewed in this section.

RNA Interference Drugs

RNA interference (RNAi) is a naturally occurring cellular mechanism for regulating gene expression mediated by small interfering RNAs.15 Synthetic small interfering RNAs can be designed to target the endogenous mRNA transcript of a given gene, leading to its cleavage and the subsequent suppression of synthesis of the encoded protein.16 Recent evidence has shown that RNAi may be a suitable approach to reduce oxalate production in PH1 patients by knocking down key enzymes involved in hepatic oxalate synthesis. Several RNAi targeting different key enzymes are currently under investigations.

One key enzyme in the hepatic oxalate synthesis is glycolate oxidase (GO), encoded by the hydroxyacid oxidase (HAO1) gene (Figure 1). GO catalyzes the oxidation of glycolate to glyoxylate, the immediate precursor to hepatic oxalate synthesis. In 2017 Liebow et al.17 published the preclinical results for ALN-GO1, a RNAi targeting hepatic GO (lumasiran), that showed...
Innovative treatment | Drug name | Phase II–III clinical trials ongoing
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RNA interference targeting glycolate oxidase | Lumasiran | Illuminate A (phase III) NCT03881184
Main inclusion criteria: age ≥ 6 yr, eGFR ≥30 ml/min
Preliminary results: 65.4% reduction of 24-h urinary oxalate at month 6; no serious adverse event reported
Estimated completion date: May 2024
Preliminary results: 65% reduction of UOx after 6 months of treatment. Consequently, prolonged treatment might be necessary before reaching a nearly normalized situation. Another important consequence could be that the systemic involvement of oxalate, especially in patients on chronic dialysis, could take longer to be cleared with this medication compared with liver transplantation. Further results from Illuminate-A and Illuminate-C trials (Table 1) are required to answer these important questions.
RNA interference targeting LDHA (Nedosiran) | PHYX03 (phase III) NCT04042402, extension of NCT03847909
Main inclusion criteria: age ≥6 yr, eGFR ≥30 ml/min per 1.73 m²
Preliminary results: NA
Estimated completion date: August 2025
Lactate dehydrogenase type 5 inhibitor | Diacomit | Phase II NCT03819647
Main inclusion criteria: age ≥6 mo, GFR ≥45 ml/min
Preliminary results: NA
Estimated completion date: May 2020

eGFR, estimated glomerular filtration rate; NA, not available.

With such emerging therapies, liver transplantation will hopefully no longer be required to cure the metabolic defect. Removing the burden of liver transplantation will improve survival of patients by avoiding the complications related to surgery. Moreover, quality of life will be very much improved. Indeed, current conservative treatments include, along with calcium oxalate crystallization inhibitors and pyridoxine, a massive fluid intake that can be hard to accept. 

However, it is important to note that the current data about lumasiran suggest that unlike liver transplantation, this drug does not allow complete normalization of the endogenous production of oxalate. Indeed, preliminary results from the Illuminate-A trial (Table 1) showed a 65% reduction of UOx after 6 months of treatment. Consequently, prolonged treatment might be necessary before reaching a nearly normalized situation. Another important consequence could be that the systemic involvement of oxalate, especially in patients on chronic dialysis, could take longer to be cleared with this medication compared with liver transplantation. Further results from Illuminate-A and Illuminate-C trials (Table 1) are required to answer these important questions.

RNAi drugs targeting GO should be available within 1 to 2 years, maybe earlier. Ideally, while awaiting US Food and Drug Administration approval and commercialization, all PH1 patients should have early access to these drugs through clinical trials or medical need programs (that are currently available for both lumasiran and nedosiran). Unfortunately, these drugs,
which need to be taken lifelong, will probably be unavailable for many patients with PH1. Indeed, it can be anticipated that the cost of these drugs will be unaffordable for some healthcare systems, especially in emerging countries where PH1 is more prevalent (>10% in some North African and Middle Eastern nations). Transplant and nephrology communities should pay close attention so that PH1 patients from emerging countries are not excluded from this important medical advance.

WHO WILL STILL NEED A KIDNEY TRANSPLANT?

Hopefully, these emerging therapies will improve the outcome of PH1 patients and reduce the prevalence of ESRD associated with PH1. For patients with CKD stages 1 to 3b (eGFR > 30 mL/min per 1.73 m² BSA) it can be expected that correcting the metabolic liver defect will halt oxalate deposition in the kidneys, preventing further kidney function deterioration. Long-term safety and efficacy data from phase III clinical trials (Table 1) are required to assess that these innovative treatments protect PH1 patients from further kidney function deterioration (especially for those with baseline eGFR between 30 and 45 ml/min per 1.73 m²). However, in patients with CKD stages 4 and 5, preventing the liver from oxalate overproduction will probably not preclude kidneys from progressing to ESRD. Moreover, patients can still be diagnosed with PH1 through ESRD, especially adults. Those patients will ultimately require kidney transplantation in addition to these treatments. We propose new strategies for management and kidney transplantation in PH1 patients with CKD in the era of RNAi drugs (Figure 3).

CHALLENGES TO OVERCOME IN KIDNEY TRANSPLANTATION

Correcting Liver Metabolic Defect in Kidney Transplant Candidates

To the best of our knowledge, lumasiran is the only RNAi drug currently tested in PH1 patients with severe kidney dysfunction, including chronic dialysis patients (Table 1). If conclusive, lumasiran will therefore be used in PH1 kidney transplant candidates. Because lumasiran is to be continued lifelong, its impact on a patient’s immunity, interaction with immunosuppressive drugs, and also the risk of urinary tract infection will have to be assessed. Indeed, because urinary glycolate concentrations will increase importantly, it could be hypothesized that it may potentially affect the bladder microbiota.

Best Timing for Kidney Transplantation After Correction of the Metabolic Defect

Because of the high heterogeneity of the disease, the development of a standard transplant strategy is...
difficult. Indeed, the systemic oxalate load in patients might be completely different. Some patients with minor kidney function impairment can have a huge oxalate deposition, whereas others with longstanding CKD may not. Moreover, as already discussed, some patients show a good response to pyridoxine treatment that allows stabilization of kidney function. Consequently, transplantation procedures should be tailored to the particular patient.

The ultimate goal before kidney transplantation is to limit as much as possible the systemic storage of oxalate to prevent oxalate precipitation in the allograft. To reach this goal, early initiation of a treatment (e.g., RNAi drugs) that corrects the metabolic defect seems logical. In PH1 patients not on dialysis and with limited systemic oxalate storage, preemptive kidney transplantation should be proposed as soon as possible after the correction of the metabolic defect (Figure 3). In patients with severe oxalosis, kidney transplantation should be delayed until the systemic storage has decreased. However, a correct assessment of the systemic burden is challenging and is discussed below.

In PH1 patients already on renal replacement therapy in whom RNAi drugs are started, POx values should be maintained at <20 μmol/L before considering the kidney transplant procedure (Figure 3). However, this POx value is very difficult to reach in daily clinical practice and also depends on systemic oxalate storage. Moreover, non-PH1 patients on chronic dialysis often show a POx value > 20 μmol/L, suggesting that this target value might be too low. Until now, intensive hemodialysis strategies were used (daily sessions of [high-flux] hemodialysis, nocturnal hemodialysis, or, mainly in small children, a combination of hemodialysis and nocturnal peritoneal dialysis) to maintain POx during interdialysis sessions below 30–45 μmol/L, the threshold of calcium oxalate supersaturation. After correcting the metabolic defect, some authors suggest that conventional hemodialysis could be sufficient to maintain POx values < 20 μmol/L. Recurrence of oxalate nephropathy on the kidney allograft might remain a concern even after the correction of the metabolic defect.

The US Renal Data System study provided important data about the evolution of POx and UOx levels after combined liver–kidney transplantation. Indeed, although POx levels dropped rapidly, UOx levels dropped slowly and progressively (with a median slope of −0.35 mmol/24 h per year). After 3 years, 36% of combined kidney–liver recipients still had hyperoxaluria. This indicates that systemic storage takes years to be cleared after correction of the metabolic defect. Consequently, the kidney allograft may still be at risk for oxalosis long after the correction of the metabolic defect because of persistent oxalate release and subsequent risk of oxalate deposition in the renal parenchyma. Therefore, it is essential to closely monitor UOx and POx after kidney transplantation and to continue applying hyperhydration and crystallization inhibitor intake to protect the new kidney allograft from oxalate deposition until normalization of POx and UOx.

Management With Hemodialysis after Kidney Transplantation

The benefit of performing hemodialysis after kidney transplantation is debatable. It is suggested that it should be limited to patients with significant systemic oxalate involvement when urine excretion is limited and for patients with acute tubular necrosis or delayed graft function. Some teams systematically perform hemodialysis after kidney transplantation in PH1 patients (Abdelaziz A, Nishio-Lucar A, Doyle A, et al. Successful management of simultaneous liver-kidney transplant recipient with primary hyperoxaluria using intensive continuous dialysis [abstract]. Available at: https://atcmeetingabstracts.com/abstract/successful-management-of-simultaneous-liver-kidney-transplant-recipient-with-primary-hyperoxaluria-using-intensive-continuous-dialysis/. Accessed July 31, 2020.). Others monitor POx levels and apply hemodialysis until levels fall under 20 μmol/L.

Can We Predict or Prevent Oxalate Deposition in the Allograft?

Assessing the Oxalate Bone Burden

Recurrence of oxalate nephropathy on the kidney allograft depends on the level of systemic oxalate storage. Thus, assessing the storage burden could be helpful in evaluating the risk of oxalate deposits in the transplanted kidney and also in determining the best timing to plan the kidney transplant procedure (Figure 3).

As previously discussed, at an advanced stage of the disease nearly all organs could be impacted by oxalate deposition, predominantly bone, kidneys, skin, retina, myocardium, vessel walls, and central nervous system. Therefore, assessment of the oxalate systemic burden in PH1 kidney transplant candidates should include ultrasound of the kidneys, extensive skin examination, neurologic exam, monitoring of the eye involvement by fundoscopy, assessment of cardiac involvement by electrocardiogram and ultrasound, and assessment of bone involvement. POx monitoring could also be useful because markedly increased POx values are observed in PH1 patients with advanced CKD who have systemic oxalosis.
Importantly, the bone compartment is the most common organ involved in systemic oxalosis. Bone can store massive amounts of oxalate. The threshold of GFR at which this systemic bone storage occurs is still debated but could be as high as 30 to 45 ml/min per 1.73 m² of BSA. Because oxalate is mobilized primarily from the bone compartment where it is stored, assessing the bone burden would provide an interesting evaluation of the risk of oxalate precipitation. Bone biopsy, although considered the reference standard for bone evaluation, is, however, invasive and rarely performed in daily clinical follow-up. Moreover, even if some case series described histologically the bone impairment in PH1 patients, little is known about the correlation of oxalate bone deposits and clinical renal outcomes after transplantation. Reports of imaging techniques such as peripheral quantitative computed tomography or biologic biomarkers such as fibroblast growth factor 23 have been proposed to non-invasively estimate bone oxalate storage, but the numbers of patients involved in these investigations were low, and none of these techniques is currently validated. Prospective longitudinal studies are required to assess the best radiologic and/or biologic and/or histologic tool that will reflect the oxalate burden and its potential response to dialysis and/or transplantation.

Native Kidney Removal

Because native kidneys are target organs of oxalate systemic storage, some centers propose bilateral native kidney removal during transplantation. Some reports have suggested its efficacy to decrease POx rapidly after combined liver–kidney transplantation. A larger case series published by Lee et al. reported on 3 PH1 pediatric patients (ages 22 months, 6.4 years, and 13.4 years, respectively) who underwent combined liver–kidney transplantation associated with bilateral nephrectomy in the same operative time. The patients were all on dialysis before transplantation (2 on hemodialysis and 1 on hemodialysis and peritoneal dialysis). All patients received postoperative hemodialysis until the POx level fell to below 20 µmol/L (6, 18, and 43 days, respectively). No complication from native nephrectomy was observed. After a follow-up of 6.5 to 8.9 years, all patients were alive with stable kidney and liver function.

However, the potential usefulness of this procedure is controversial and debatable. Indeed, in addition to increasing the surgical intervention time, it could be hypothesized that in anuric PH1 patients kidney stones can no longer dissolve and reach the circulation. Further prospective studies including larger cohorts are needed to assess the efficacy and safety of such operative procedures.

OTHER PERSPECTIVES

In addition to the new drugs currently involved in clinical trials, other therapeutic perspectives in PH1 are in development and are discussed in this section.

Oxalate-Degrading Bacteria

The intestinal tract of humans is usually colonized by anaerobic oxalate-degrading bacteria such as Oxalobacter formigenes, which uses oxalate as its sole source of energy; animal models have shown that endogenous oxalate can be eliminated via the intestinal tract. Two pilot trials have shown the efficacy of orally administered Oxalobacter in patients with PH with normal renal function or ESRD. However, these promising results were not confirmed in a phase III trial. Nonetheless, another phase III clinical trial is ongoing to evaluate the efficacy and safety of Oxalobacter in PH patients. Recently, interim results from a phase II open-label trial that evaluated the efficacy and safety of the long-term administration (24 months) of O formigenes (Oxabact; OxThera AB, Stockholm, Sweden) in PH1 patients on chronic dialysis were presented. These results showed significant reductions in POx values over time and improvement of systemic oxalate deposition in the 8 PH1 patients treated without significant side effects. Moreover, a recent case report showed that treatment with O formigenes combined with intensive dialysis led to a reduction of POx, stabilization of systemic oxalosis, and improvement in the clinical disease course in a female anuric PH1 infant. If these promising results are confirmed in phase III trials, some alternative strategies could be considered and tested in a near future, such as combining O formigenes and RNAi drugs in patients with severe systemic oxalosis. However, O formigenes has not yet been tested in immunosuppressed patients. Caution is required regarding the chronic administration of a bacteria in a kidney transplant recipient on immunosuppressors.

Chaperone Molecules

Some missense mutations generate a strong N-terminal mitochondrial targeting sequence that directs AGT to mitochondria. Although mutant AGT is functional, it is inefficient because the enzyme must be in the peroxisome to detoxify glyoxylate (Figure 1). In 2014 Miyata et al. showed in vitro that exposure to dequalinium chloride restores trafficking of mutant AGT from mitochondria to peroxisomes with a subsequent reduction in oxalate levels. Other in vitro data showed that prolonged treatment with the translation elongation inhibitor emetine, a medicinal alkaloid used in the treatment of amoebiasis, could correct D170R-AGT mislocalization and reduce the augmented oxalate level in culture media of patient-derived hepatocytes.
bearing the Gly170Arg mutation. To the best of our knowledge, no animal or human trial has been published with such chaperone molecules so far.

**Gene Therapy**

Recently, it has been shown to be possible to reprogram mature somatic cells to generate induced pluripotent stem cells (iPSCs). These iPSCs can further differentiate in many cell types, including liver cells. Recently, Estève et al. were able to generate *in vitro* transgene-free iPSCs after reprogramming dermal fibroblasts from a PH1 patient. PH1-iPSCs could further be differentiated into hepatocyte-like cells that displayed a low residual AGT expression. They were able to rescue *in vitro* AGT expression in PH1–hepatocyte-like cells after transduction with a lentiviral vector expressing a codon-optimized AGT cDNA. The same team recently reported that with the use of the clustered regularly interspaced short palindromic repeats/Cas9 nuclease technique, it was possible to integrate a phosphoglycerate kinase promoter-driven codon-optimized AGT transgene to the AAVS1 site (an open chromosomal region on human chromosome 19 that allows the safe insertion of an exogenous gene) of iPSCs generated from a PH1 patient to rescue AGT expression after differentiation into hepatocyte-like cells.

Another team also showed that it was possible to inhibit the *HAO1* gene (encoding GO) using clustered regularly interspaced short palindromic repeats/Cas9, leading to the reduction of UOX levels to normal levels and prevent nephrocalcinosis formation without toxic effects in a murine PH1 model.

Delivery of a normal AGXT gene through viral vectors is also in preclinical development. Adeno-associated virus 5 and 8 vectors have shown their efficacy to reduced UOX in PH1 mice models. I.v. administration of SVac (a vector derived from macaque polyomavirus SV40) in mice and nonhuman primates resulted in the expression of an applied gene in the liver. Because PH1 is associated with a liver-specific gene defect, PH1 patients could benefit from this treatment. These exciting proofs of concept could serve as the basis of future therapeutic options, but much research is still necessary before clinical application.

**CONCLUSIONS**

Undoubtedly, the management of kidney transplant candidates and recipients will be profoundly modified in the near future with the emergence of innovative drugs, notably RNAi drugs. Liver transplantation will no longer be necessary to treat the liver metabolic defect associated with PH1, improving significantly patient survival and quality of life. Still, some patients will require kidney transplantation, and their management will remain challenging. Developing better tools to evaluate the systemic oxalate burden will help delineate the best timing for kidney transplantation to avoid oxalate deposition recurrence in the kidney allograft. Questions regarding these new treatments and the outcome of kidney allograft, interactions with immunosuppressive drugs, and long-term complications need to be rapidly answered.

**DISCLOSURE**

AD is a principle investigator Alnylam. PC is a principle investigator and Scientific Advisory Board for Alnylam, Dicerna, and Oxthera. All the other authors declared no competing interests.

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