Long-Term Transplantation Outcomes in Patients With Primary Hyperoxaluria Type 1 Included in the European Hyperoxaluria Consortium (OxalEurope) Registry

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Introduction: In primary hyperoxaluria type 1 (PH1), oxalate overproduction frequently causes kidney stones, nephrocalcinosis, and kidney failure. As PH1 is caused by a congenital liver enzyme defect, combined liver–kidney transplantation (CLKT) has been recommended in patients with kidney failure. Nevertheless, systematic analyses on long-term transplantation outcomes are scarce. The merits of a sequential over combined procedure regarding kidney graft survival remain unclear as is the place of isolated kidney transplantation (KT) for patients with vitamin B6-responsive genotypes.

Methods: We used the OxalEurope registry for retrospective analyses of patients with PH1 who underwent transplantation. Analyses of crude Kaplan–Meier survival curves and adjusted relative hazards from the Cox proportional hazards model were performed.

Results: A total of 267 patients with PH1 underwent transplantation between 1978 and 2019. Data of 244 patients (159 CLKTs, 48 isolated KTs, 37 sequential liver–K Ts [SLKTs]) were eligible for comparative analyses. Comparing CLKTs with isolated KTs, adjusted mortality was similar in patients with B6-unresponsive genotypes but lower after isolated KT in patients with B6-responsive genotypes (adjusted hazard ratio 0.07, 95% CI: 0.01–0.75, \( P = 0.028 \)). CLKT yielded higher adjusted event-free survival and death-censored kidney graft survival in patients with B6-unresponsive genotypes (\( P = 0.025, P < 0.001 \)) but not in patients with B6-responsive genotypes (\( P = 0.145, P = 0.421 \)). Outcomes for 159 combined procedures versus 37 sequential procedures were comparable. There were 12 patients who underwent pre-emptive liver transplantation (PLT) with poor outcomes.

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Received 21 September 2021; revised 28 October 2021; accepted 1 November 2021; published online 26 November 2021
**Conclusion:** The CLKT or SLKT remains the preferred transplantation modality in patients with PH1 with B6-unresponsive genotypes, but isolated KT could be an alternative approach in patients with B6-responsive genotypes.

*Kidney Int Rep* (2022) 7, 210–220; https://doi.org/10.1016/j.ekir.2021.11.006

**KEYWORDS:** combined liver-kidney transplantation; graft survival; primary hyperoxaluria; sequential liver-kidney transplantation

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**PH1** is a rare autosomal recessive disease characterized by hepatic overproduction of oxalate,6 which is primarily excreted by the kidneys.2 Excessive amounts of urinary oxalate often result in calcium-oxalate kidney stone formation, nephrocalcinosis, and kidney failure.3 In patients with kidney failure, renal excretion of oxalate decreases, which leads to oxalate accumulation in various tissues causing multiorgan disease. This life-threatening situation is referred to as systemic oxalosis.4,5 Currently, orthotopic liver transplantation is the only available treatment that ends oxalate overproduction in patients with PH1 at the price of removing an otherwise perfectly functioning liver.6 New promising treatment options, using RNA interference (RNAi) technology, may reduce the need for liver transplantation in the future,7 but long-term prospects are unknown.

Current PH1 treatment guidelines regarding transplantation strategies are based on ungraded statements or expert opinions,8,9 as randomized controlled trials are not feasible as a research field of organ transplantation. According to the European guideline, the transplantation method of choice in PH1 is CLKT once advanced kidney failure has developed.8 Nevertheless, there is ongoing discussion on the merits of a two-step procedure, referred to as SLKT.10,11 To date, studies have not found significant differences in patient or graft survival between CLKT and SLKT in patients with PH1.12–14 The choice between CLKT and SLKT is based on the patient’s condition and local facilities8 and the availability of a living donor.11 Liver transplantation before the development of end-stage kidney disease (ESKD; isolated PLT) is ethically arguable owing to the unpredictability of the individual disease course15,16 and the considerable risks of an orthotopic liver transplantation procedure including a reported mortality rate of 15% to 20% within the first year,17,18 notwithstanding the risks and complications of lifelong immune suppression, and now the prospects of novel oxalate-reducing therapies could compound this. Unsurprisingly, therefore, PLT is not widely used.8

Isolated KT is generally regarded as obsolete in individuals with PH1-associated ESKD, because unabated production of oxalate will lead to rapid graft loss owing to recurrent oxalate depositions in 90% to 100% of patients.19 Nevertheless, this approach has been suggested for a subset of patients with PH1 who respond well to supraphysiological doses of vitamin B6.20,21 Vitamin B6 is a coenzyme of the defective liver enzyme alanine-glyoxylate aminotransferase and overcomes the misfolding and dimerization defects associated with certain mutations in the *AGXT* gene (most often p.Gly170Arg), allowing correct peroxisomal targeting. This may result in partial to complete normalization of urinary oxalate excretion. Purely based on this pathophysiological rationale, KT could be considered for selected patients with B6-responsive *AGXT* genotypes.8

Because recommendations on performing KT or SLKT in selected patients are based on small case series,13,20 the European guideline is cautiously formulated and may lead to different interpretations in clinical practice. We now focused on the clinically relevant comparison of long-term outcomes after CLKT versus KT in patients biallelic for 3 frequently found and profoundly vitamin B6-responsive *AGXT* genotypes (p.Gly170Arg, p.Phe152Ile, and p.Ile244Thr; abbreviated here as short B6 positive [B6+] patients) versus patients with all other *AGXT* genotypes (termed here as short B6 negative [B6−] patients). Second, we compared outcomes of CLKT versus SLKT. Data retrieved from the OxalEurope registry, one of the largest PH registries worldwide and including information on >1100 patients, of whom 993 patients had PH1, were analyzed.

**METHODS**

**Study Population**

This was a retrospective cohort study. All patients with PH1 in the OxalEurope registry as of March 9, 2021, who underwent one or more liver or kidney transplantation(s) were identified. Informed consent was obtained if applicable. For patients residing in the United Kingdom, additional follow-up data were retrieved from the UK Transplant Registry. We extracted the following data from the OxalEurope registry: sex, date of birth, country of origin and...
RESULTS
Patient Cohort
Table 1 reveals the characteristics of patients with PH1 (N = 267) from 8 countries. CLKT was performed in 159, KT in 59, SLKT in 37, and PLT in 12 patients, respectively. The median age at diagnosis was 7.6 (interquartile range [IQR]: 0.8–20.4) years, and age at transplantation before the year 2000 or the year 2010 when comparing CLKT with SLKT.

All tests were two sided with a significance level of P < 0.05, using IBM SPSS version statistics 26 (Armonk, NY) and R (version 3.6.1).

Table 1. Clinical characteristics of the European PH1 cohort

| Characteristics                          | n (%)/median (IQR) | Availability (n) |
|-----------------------------------------|--------------------|------------------|
| **Sex**                                  |                    |                  |
| - Male                                   | 145 (54.3)         | 267              |
| - Female                                 | 122 (45.7)         |                  |
| **Country of residency**                 |                    |                  |
| - United Kingdom                         | 53 (19.9)          |                  |
| - France                                 | 66 (24.7)          |                  |
| - Germany                                | 68 (25.5)          |                  |
| - The Netherlands                        | 36 (13.5)          |                  |
| - Italy                                  | 21 (7.9)           |                  |
| - Belgium                                | 12 (4.5)           |                  |
| - Switzerland                            | 9 (3.4)            |                  |
| - Russia                                 | 2 (0.7)            |                  |
| **AGXT genotype**                        | 211                |                  |
| - B6 responsive                          | 46 (21.6)          |                  |
| - p. Gly170Arg                           | 33 (15.6)          |                  |
| - p. Ile244Thr                           | 9 (4.3)            |                  |
| - p. Phe152Ile                           | 2 (0.9)            |                  |
| - Combination of above                   | 2 (0.9)            |                  |
| - B6 unresponsive                        | 165 (78.2)         |                  |
| **Age at first symptoms, yr**            | 4.0 (0.5–12.4)     | 216              |
| **Age at diagnosis, yr**                 | 7.6 (0.8–20.4)     | 208              |
| **Infantile oxalosis**                   | 55 (21.9)          | 251              |
| **Clinical findings at time of diagnosis:**|                    |                  |
| - Nephrocalcinosis                       | 134 (66.7)         | 201              |
| - Urolithiasis                           | 142 (66.4)         | 214              |
| - ESKD                                   | 143 (59.8)         | 239              |
| - Systemic oxalosis                      | 22 (23.9)          | 92               |
| **Age at ESKD, yr**                      | 15.5 (9.9–26.0)    | 200              |
| **Dialysis vintage, yr**                 | 1.4 (0.7–2.6)      | 152              |
| **Age at transplantation, yr**           | 16.8 (3.9–28.9)    | 233              |
| **Period of transplantation**            | 238                |                  |
| - Before 2000                            | 83 (34.9)          |                  |
| - Between 2000 and 2010                  | 83 (34.9)          |                  |
| - After 2010                             | 72 (30.3)          |                  |
| **Type of first transplant**             | 267                |                  |
| - CLKT                                   | 159 (59.6)         |                  |
| - KT                                     | 59 (22.1) a        |                  |
| - SLKT                                   | 37 (13.9)          |                  |
| - PLT                                    | 12 (4.5)           |                  |
| **Follow-up, yr**                        | 6.0 (1.9–11.5)     | 267              |

CLKT, combined liver–kidney transplantation; ESKD, end-stage kidney disease; IQR, interquartile range; KT, kidney transplantation; PH1, primary hyperoxaluria type 1; PLT, pre-emptive liver transplantation; SLKT, sequential liver-kidney transplantation.

aGenotype was known in 46 of 59 KT recipients.
Table 2. Characteristics of patients with PH1 who underwent KT or CLKT

| Characteristics                      | B6-responsive patients (n = 41) | B6-unresponsive patients (n = 126) |
|--------------------------------------|---------------------------------|-----------------------------------|
| CLKT (n = 20)                        | Availability (n)                | Isolated KT (n = 21)              |
| CLKT (n = 99)                        | Availability (n)                | Isolated KT (n = 27)              |
| Sex, n (%)                           |                                 |                                   |
| - Male                               | 11 (55.0)                       | 9 (42.9)                          |
| - Female                             | 9 (45.0)                        | 12 (57.1)                         |
| Age at diagnosis, yr, median (IQR)   | 20.4 (0.3–42.5)                 | 30.8 (17.3–40.7)                  |
| Infante oxalosis, n (%)              | 4 (22.2)                        | 0 (0)                             |
| Age at ESKD, yr, median (IQR)        | 20.3 (0.3–45.7)                 | 31.3 (17.2–48.1)                  |
| ESKD at time of diagnosis, n (%)     | 14 (77.8)                       | 18 (80)                           |
| Systemic oxalosis at time of diagnosis, n (%) | 0 (0) | 3 (1.9–4.0) |
| Dialysis vintage, yr, median (IQR)   | 1.4 (0.8–2.6)                   | 3.5 (1.9–4.0)                     |
| Age at transplantation, yr, median (IQR) | 21.0 (2.9–48.8) | 34.8 (22.4–51.7)                   |
| Period of transplantation, n (%)     |                                 |                                   |
| - Before 2000                        | 3 (15)                          | 8 (50)                            |
| - Between 2000 and 2010              | 5 (35.7)                        | 5 (31.3)                          |
| - After 2010                         | 6 (42.9)                        | 3 (18.8)                          |
| Follow-up period, yr, median (IQR)   | 7.4 (6.0–10.7)                  | 10.2 (4.2–26.3)                   |
| **P value**                          |                                 |                                   |
| CLKT (n = 20)                        | 0.437                           |                                   |
| CLKT (n = 99)                        | 0.166                           |                                   |

CLKT, combined liver kidney transplantation; ESKD, end-stage kidney disease; IQR, interquartile range; KT, kidney transplantation; PH1, primary hyperoxaluria type 1.

These patients were on dialysis for a few years before KT and received CLKT after failed KT. Data from 244 patients were used for comparative analyses; patients with an isolated PLT were not included (n = 12).
Figure 1. Kaplan–Meier survival analyses comparing CLKT with KT in patients with PH1 with B6+ and B6− mutations. CLKT, combined liver–kidney transplantation; KT, kidney transplantation; PH1, primary hyperoxaluria type 1. (a,b) Patient survival; (c,d) event-free survival; and (e,f) death-censored kidney graft survival.
oxalosis or in subgroup analyses with only patients who received their first transplant after January 1, 2000 or 2010 (Supplementary Figures S2–S4). This remained the same after correcting for confounders (Supplementary Table S2).

PLT
Characteristics of patients with PH1 who underwent PLT, which, by definition, was performed before development of ESKD, are described in Supplementary Table S3. There were 2 patients who died, 2 developed ESKD, and the remaining 8 survived with a functioning liver graft at a median follow-up of 5.7 (IQR: 2.0–11.0) years.

Causes of Death
A total of 52 of 267 patients were deceased at the time of assessment (31 of 165 B6−, 10 of 46 B6+, 11 oxalosis or in subgroup analyses with only patients who received their first transplant after January 1, 2000 or 2010 (Supplementary Figures S2–S4). This remained the same after correcting for confounders (Supplementary Table S2).

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unknown AGXT genotype), of whom 28 after CLKT (17.6%), 16 after KT (27.1%), 6 after SLKT (16.2%), and 2 after PLT (16.7%). Death occurred at a median age of 20.4 (IQR: 3.3–40.6) years. For patients who died after CLKT, death occurred 0.1 (IQR: 0.04–1.2) year after CLKT; the cause of death was reported for 13 cases (46%) and related to either a postoperative event \((n = 11)\) or complication of immunosuppressive treatment \((n = 2)\). Of 59 patients who underwent KT, 16 (27.1%) died (5 B6+, 5 B6−, 6 unknown AGXT genotype). In patients who died after KT, transplantation was performed before 2000 in all but 4 cases. Median time between KT and death was 7.1 (IQR: 2.9–12.6) years. Cause of death was known in 10 cases and reported as multiorgan failure in all of them, with “systemic oxalosis” explicitly mentioned in 5 cases (1 B6+, 1 B6−, 3 unknown AGXT genotype). The B6+ patient had manifestations of systemic oxalosis at diagnosis and a plasma oxalate level of 156 μmol/l. He experienced kidney graft failure after 2 weeks owing to oxalate deposition and died 4 years after owing to cardiac failure related to systemic oxalosis. The B6− patient experienced kidney graft failure after 1.4 years and died 10 years after. Of the 37 patients, 6 (16.2%) died after liver transplantation, of whom 3 died within 6 months owing to liver graft failure. Of the 12 patients receiving PLT, 2 died, both owing to liver graft failure without development of ESKD, at 2.9 and 11.0 years after transplantation.

**DISCUSSION**

In this long-term outcome study of a large cohort of transplanted patients with PH1, we found significantly higher event-free survival and death-censored kidney graft survival after CLKT than after KT for B6+ patients, but we did not find such benefit for CLKT over KT in B6− patients. Outcomes of CLKT and SLKT were comparable. The outcomes of 12 pre-emptive isolated liver transplantations were unfavorable and do not support this approach. Median age at transplantation was 16.8 years. In all groups, 10-year patient survival was approximately 80%. This high mortality at a young age indicates the severity of PH1.

**CLKT Versus KT in B6− Patients**

Our data vindicate the general recommendation of performing CLKT in B6− patients with PH1 and ESKD. Previous studies that described long-term transplantation outcomes in patients with PH1 have reported evident superiority of CLKT over KT. Nevertheless, B6 responsiveness was not reported in any of these studies. Because hepatic overproduction of oxalate continues unabated after KT in B6− patients, this procedure cannot be recommended.

**CLKT Versus KT in B6+ Patients**

In B6+ patients, patient survival was higher post-KT after correcting for confounders (adjusted hazard ratio 0.07, 95% CI, 0.01–0.75, \(P = 0.028\); Supplementary Table S1). (Un)adjusted event-free survival rates were not statistically different between CLKT and KT in this patient group. Although unadjusted death-censored kidney graft survival was superior after CLKT as compared with KT, this difference became insignificant after adjusting for confounding factors (Supplementary Table S1). In our recent review of literature on transplantation outcomes in PH, we identified only 1 previous study reporting AGXT genotypes of transplanted patients with PH1. Lorenz et al. described a case series of 5 B6− patients who received KT at a median age of 39 years and who experienced successful outcomes, even though 1 patient was diagnosed only after receiving KT. The report by Lorenz et al. and our findings point to KT as a serious alternative to CLKT in patients with B6+ genotypes.

**CLKT Versus SLKT**

Our data revealed no differences in PH1 patient survival, event-free survival, nor death-censored kidney graft survival between CLKT and SLKT. Recently, Xiang et al. analyzed a large cohort of 181 CLKT recipients and 20 patients who underwent SLKT. They reported cumulative 5-year patient and kidney graft survival rates of 77% and 78.1% for CLKT and 84.1% and 85.0% for SLKT, respectively. These survival rates are similar to those in our cohort. Nevertheless, all patients included by Xiang et al. received both liver and kidney transplants, whereas we included all patients planned to receive SLKT, including those who died after liver transplantation and before KT. Other studies, all single-center experiences, have also failed to reveal the merits of a sequential procedure regarding kidney graft survival. Nevertheless, there may be other compelling reasons to perform a sequential procedure instead of a combined procedure. In case of infantile oxalosis, a combined procedure may not be feasible, though successful combined procedures have been described in 14 children with PH1, including 8 infants who weighed <15 kg at the time of CLKT. Second, if the recipient has developed systemic oxalosis, imminent kidney graft failure owing to hyperoxaluria resulting from mobilization of oxalate stores may be averted when performing SLKT. In contrast, one could also argue that a functional kidney transplant removes the excessive amount of oxalate more effectively than chronic dialysis treatment,

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CLINICAL RESEARCH

Pre-Emptive Liver Transplantation

Brinkert et al. previously reported the beneficial results of PLT with 100% patient and liver graft survival in a series of only 4 patients. We found no larger studies on the outcomes of PLT. The considerable mortality of PLT in our series (16.7%) together with the progression to ESKD after PLT (16.7%) does not support this transplantation strategy in patients with PH1.

Strengths and Limitations

The strengths of our study are the large number of patients and the fact that genotype was known for most patients, which enabled us to compare transplantation strategies in patients with vitamin B6+ versus B6− mutations. Certain limitations of this study must, however, be taken into consideration. First, our findings are based on retrospective analyses. Our series covers multiple decades across many countries with varying medical practices. Data on standard transplantation care, including perioperative dialysis schedules, were rarely reported. Nonuniform practice in peritransplant care may have influenced the results. Second, as common in registries, not all patient characteristics were registered for all patients, and some characteristics were not captured by the registry at all (e.g., donor age and immunosuppression management). Furthermore, full screening for systemic oxalosis was performed in one-third of the patients only. This is further complicated by the lack of validated screening assessments (especially for bone manifestations) and scoring systems to evaluate severity. Asymptomatic patients may already have developed manifestations of systemic oxalosis, which most often remain unnoticed unless active screening has been undertaken. Finally, our analyses were based on presumed B6-responsiveness related to AGXT genotype. We chose this approach because a definition of clinical B6 response in patients who present with severe kidney failure is not well established. Urinary oxalate excretion is unavailable in patients with anuria and unreliable in patients with ESKD because oxalate is partly deposited in the tissues instead of being excreted in the urine. In patients who do actually respond to B6 with decrease of endogenous oxalate production, a decrease in plasma oxalate may be hampered owing to release of systemically stored oxalate. Besides, interpretation of plasma oxalate values is complicated by the lack of consensus on reference values both owing to differences in laboratory techniques and owing to the paucity of data on plasma oxalate levels in patients with ESKD without PH. Finally, plasma glycolate levels were rarely available in the registry because only 3 laboratories measure plasma glycolate. Therefore, we think that our approach mimics the actual clinical situation in which physicians are faced with patients with PH1 with advanced kidney failure at the time of diagnosis in whom they can only rely on presumed B6 responsiveness, based on the underlying mutation.

Impact in the Light of Upcoming RNAi Drugs

New drugs that target the source of the disease are emerging. Using RNAi, these drugs inhibit hepatic enzymes in glyoxylate metabolism to lower endogenous oxalate production. One drug, Lumasiran, has already been found to effectively reduce urinary oxalate excretion in a randomized controlled trial and was recently approved by the Food and Drug Administration and the European Medicines Agency. These promising drugs will modify therapeutic management of patients with PH1 and hopefully preclude the need for liver transplantation in the near future. Nevertheless, long-term efficacy in preventing kidney failure
and the occurrence of long-term side effects are unknown. In clinical trials of these drugs, not all patients were found to have normalization of urinary oxalate excretion and it has been suggested that liver transplantation may clear a high oxalate storage sooner than new medications. Further review is needed to consider the need for lifelong RNAi treatment in B6+ patients, especially in situations where the high costs of RNAi therapeutics may limit accessibility.

Conclusions
Our data support the premise that performing KT in selected patients with PH1 with B6-responsive mutations could be a safe alternative approach in case of kidney failure. In patients who require liver–kidney transplantation, CLKT and SLKT yielded the same outcomes. International collaboration remains crucial in gaining new insights in this intriguing disease with a fast-changing treatment landscape, aiming to provide the best possible care to individual patients and their families.

DISCLOSURE
ELM, SFG, MJSO, and JWG have received an unconditional grant from both Alnylam Pharmaceuticals and Dicerna Pharmaceuticals, not related to this work. BH is a senior medical advisor at Dicerna Pharmaceuticals. SAH has received consultation fees and travel grants from Dicerna Pharmaceuticals and Alnylam Pharmaceuticals. Alnylam and Dicerna have provided an unconditional grant to the OxalEurope Registry. All the other authors declared no competing interests.

ACKNOWLEDGMENTS
The authors thank all the patients, clinicians, and scientists who contributed to the OxalEurope Consortium. The authors thank Gill Rumsby, PhD, for identifying the mutation of the hyperoxaluria gene during her tenure at the University College London. The authors also thank the UK Transplant Registry for their contribution. This work is supported by unconditional grants from both Alnylam Pharmaceuticals and uniQure.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Table S1. Cox proportional hazard model covariates for KT versus CLKT.
Table S2. Cox proportional hazard model covariates for SLKT versus CLKT.
Table S3. Characteristics of patients with PH1 who underwent pre-emptive liver transplantation.
Table S4. Life table analyses comparing CLKT with KT in B6+ and B6− patients with PH1.
Table S5. Life table analyses comparing CLKT with SLKT in patients with PH1.

REFERENCES
1. Cochat P, Rumsby G. Primary hyperoxaluria [published correction appears in N Engl J Med. 2013;369:2168]. N Engl J Med. 2013;369:649–658. https://doi.org/10.1056/NEJMa1301564
2. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. Kidney Int. 2009;75:1264–1271. https://doi.org/10.1038/ki.2009.32
3. Mandrile G, van Woerden CS, Berchialla P, et al. Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. Kidney Int. 2014;86:1197–1204. https://doi.org/10.1038/ki.2014.222
4. Beck BB, Hoyer-Kuhn H, Göbel H, Habbig S, Hoppe B. Hyperoxaluria and systemic oxalosis: an update on current therapy and future directions. Expert Opin Investig Drugs. 2013;22:117–129. https://doi.org/10.1517/13543784.2013.741587
5. Ben-Shalom E, Cytter-Kuint R, Rinat C, et al. Long-term complications of systemic oxalosis in children—a retrospective single-center cohort study. Ped Nephrol. 2021;36:3123–3132. https://doi.org/10.1007/s00467-021-05002-1
6. Cochat P, Fargue S, Harambat J. Primary hyperoxaluria type 1: strategy for organ transplantation. Curr Opin Organ Transplant. 2010;15:590–593. https://doi.org/10.1097/MOT.0b013e32833e35f5
7. Garreffs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. N Engl J Med. 2021;384:1216–1226. https://doi.org/10.1056/NEJMo12119
8. Cochat P, Hulton SA, Acquaviva C, et al. Primary hyperoxaluria type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant. 2012;27:1729–1736. https://doi.org/10.1093/ndt/gfs078
9. Milliner DS, McGregor TL, Thompson A, et al. End points for clinical trials in primary hyperoxaluria. Clin J Am Soc Nephrol. 2020;15:1056–1065. https://doi.org/10.2215/CJN.13821119
10. Kemper MJ. Concurrent or sequential liver and kidney transplantation in children with primary hyperoxaluria type 1? Pediatr Transplant. 2005;9:693–696. https://doi.org/10.1111/j.1399-3046.2005.00362.x

Figure S1. Kaplan–Meier survival analyses comparing CLKT with KT in patients with PH1 selected on B6− patients.
Figure S2. Kaplan–Meier survival analyses comparing CLKT with SLKT in patients with PH1; transplantations were performed after January 1, 2000.
Figure S3. Kaplan–Meier survival analyses comparing CLKT with SLKT in patients with PH1; transplantations were performed after January 1, 2010.
11. Pham TA, Esquivel C. Are two operations better than one? The debate over combined versus sequential liver-kidney transplantation from a single live donor in the treatment of primary hyperoxaluria type 1. Pediatr Transplant. 2019;23:e13457. https://doi.org/10.1111/petr.13457

12. Büscher R, Büscher AK, Cetiner M, et al. Combined liver and kidney transplantation and kidney after liver transplantation in children: indication, postoperative outcome, and long-term results. Pediatr Transplant. 2015;19:858–865. https://doi.org/10.1111/petr.12595

13. Horoub R, Shamsaeefar A, Dehghani M, et al. Liver transplant for primary hyperoxaluria type 1: results of sequential, combined liver and kidney, and preemptive liver transplant. Exp Clin Transplant. 2021;19:445–449. https://doi.org/10.6002/ect.2019.0150

14. Xiang J, Chen Z, Xu F, et al. Outcomes of liver-kidney transplantation in patients with primary hyperoxaluria: an analysis of the scientific registry of transplant recipients database. BMC Gastroenterol. 2020;20:208. https://doi.org/10.1186/s12876-020-01349-1

15. Hrambat J, Fargue S, Acquaviva C, et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p. Gly170Arg AGXT mutation is associated with a better outcome. Kidney Int. 2010;77:443–449. https://doi.org/10.1038/ki.2009.435

16. Hoppe B. Evidence of true genotype-phenotype correlation in primary hyperoxaluria type 1. Kidney Int. 2010;77:383–385. https://doi.org/10.1038/ki.2009.471

17. Adam R, Karam V, Caillé V, et al. 2018 Annual Report of the European Liver Transplant Registry (ELTR)—50-year evolution of liver transplantation. Transpl Int. 2018;31:1293–1317. https://doi.org/10.1111/tri.13358

18. Hoppe B, Langman CB. A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. Pediatr Nephrol. 2003;18:986–991. https://doi.org/10.1007/s00467-003-1234-x

19. Bacchetta J, Cochat P. Primary disease recurrence—effects on paediatric renal transplantation outcomes. Nat Rev Nephrol. 2015;11:371–384. https://doi.org/10.1038/nrneph.2015.54

20. Lorenz EC, Lieske JC, Seide BM, et al. Sustained pyridoxine response in primary hyperoxaluria type 1 recipients of kidney alone transplant. Am J Transplant. 2014;14:1433–1438. https://doi.org/10.1111/ajt.12706

21. van Woerden CS, Groothoff JW, Wijburg FA, Annink C, Wanders RJ, Waterham HR. Clinical implications of mutation analysis in primary hyperoxaluria type 1. Kidney Int. 2004;66:746–752. https://doi.org/10.1111/j.1523-1755.2004.00796.x

22. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2020;97:1117–1129. https://doi.org/10.1016/j.kint.2020.02.010

23. Fargue S, Rumsby G, Danpure CJ. Multiple mechanisms of action of pyridoxine in primary hyperoxaluria type 1. Biochim Biophys Acta. 2013;1832:1776–1783. https://doi.org/10.1016/j.bbadis.2013.04.010

24. Compagnon P, Metzler P, Samuel D, et al. Long-term results of combined liver-kidney transplantation for primary hyperoxaluria type 1: the French experience. Liver Transpl. 2014;20:1475–1485. https://doi.org/10.1002/lt.24009

25. Hrambat J, van Stralen KJ, Espinosa L, et al. Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. Clin J Am Soc Nephrol. 2012;7:458–465. https://doi.org/10.2215/CJN.07430711

26. Metry EL, van Dijk LMM, Peters-Sengers H, et al. Transplantation outcomes in patients with primary hyperoxaluria: a systematic review. Pediatr Nephrol. 2021;36:2217–2226. https://doi.org/10.1007/s00467-021-05043-6

27. Ozer A, Aktas H, Bolum B, Emirgöl R. The experience of combined and sequential liver and kidney transplantation from a single living donor in patients with primary hyperoxaluria type 1. Pediatr Transplant. 2019;23:e13406. https://doi.org/10.1111/petr.13406

28. Duclaux-Loras R, Bacchetta J, Berthiller J, et al. Pediatric combined liver-kidney transplantation: a single-center experience of 18 cases. Pediatr Nephrol. 2016;31:1517–1529. https://doi.org/10.1007/s00467-016-3324-6

29. Narasimhan G, Govil S, Rajalingam R, Venkataraman C, Shanmugam NP, Rela M. Preserving double equipoise in living donor-liver-kidney transplantation for primary hyperoxaluria type 1. Liver Transpl. 2015;21:1324–1326. https://doi.org/10.1002/lt.24167

30. Mor E, Nesher E, Ben-Ari Z, et al. Sequential liver and kidney transplantation from a single living donor in two young adults with primary hyperoxaluria type 1. Liver Transpl. 2013;19:646–648. https://doi.org/10.1002/lt.23642

31. Sasaki K, Sakamoto S, Uchida H, et al. Two-step transplantation for primary hyperoxaluria: a winning strategy to prevent progression of systemic oxalosis in early onset renal insufficiency cases. Pediatr Transplant. 2015;19:E1–E6. https://doi.org/10.1111/petr.12376

32. Brinkert F, Ganschow R, Helmke K, et al. Transplantation procedures in children with primary hyperoxaluria type 1: outcome and longitudinal growth. Transplantation. 2009;87:1415–1421. https://doi.org/10.1097/TP.0b013e3181a27939

33. Stokes F, Acquaviva-Bourdain C, Hoppe B, et al. Plasma oxalate: comparison of methodologies. Urolithiasis. 2020;48:473–480. https://doi.org/10.1007/s00240-020-01197-4

34. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO. Primary hyperoxaluria type 1: still challenging!. Pediatr Nephrol. 2006;21:1075–1081. https://doi.org/10.1007/s00467-006-0124-4

35. Hoyer-Kuhn H, Kohbrok S, Volland R, et al. Vitamin B6 in primary hyperoxaluria I: first prospective trial after 40 years of practice. Clin J Am Soc Nephrol. 2014;9:468–477. https://doi.org/10.2215/CJN.08820613

36. Singh P, Chebib FT, Cogal AG, Gavrilov DK, Harris PC, Lieske JC. Pyridoxine responsiveness in a type 1 primary hyperoxaluria patient with a rare (atypical) AGXT gene mutation. Kidney Int Rep. 2020;5:955–958. https://doi.org/10.1016/j.ekir.2020.04.004

37. van Harskamp D, Garrelfs SF, Oosterveld MJS, Groothoff JW, van Goudoever JB, Schierbeek H. Development and
validation of a new gas chromatography-tandem mass spectrometry method for the measurement of enrichment of glyoxylate metabolism analytes in hyperoxaluria patients using a stable isotope procedure. Anal Chem. 2020;92:1826–1832. https://doi.org/10.1021/acs.analchem.9b03670

38. ClinicalTrials.gov. Study to Evaluate Lumasiran in Children and Adults With Primary Hyperoxaluria Type 1 (ILLUMINATE-A). https://clinicaltrials.gov/ct2/show/NCT03681184. Accessed September 21, 2021.

39. Devresse A, Cochat P, Godefroid N, Kanaan N. Transplantation for primary hyperoxaluria type 1: designing new strategies in the era of promising therapeutic perspectives. Kidney Int Rep. 2020;5:2136–2145. https://doi.org/10.1016/j.ekir.2020.09.022