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CLINICAL RESEARCH

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–KTs [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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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.

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PH1 is a rare autosomal recessive disease characterized by hepatic overproduction of oxalate,[1] 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 facilities[8] 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 course[15,16] 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

residence, *AGXT* genotype, symptoms at presentation, age at first symptom(s), diagnosis and ESKD (defined as chronic kidney disease stage 5 or 5 D[22]), manifestations of systemic oxalosis, plasma oxalate levels, dialysis modality, date of transplantation, transplant type, date of transplant failure, and follow-up data. Patients with a delayed PH1 diagnosis (i.e., established after first KT) were excluded ($n = 37$) as comparison of transplantation strategies in patients with established PH was the aim of this study. Infantile oxalosis was defined as the development of ESKD before the age of 1 year.[21] Patients homozygous for the following *AGXT* mutations were deemed to be B6+: p.Gly170Arg ($n = 33$), p.Ile244Thr ($n = 9$), or p.Phe152Ile ($n = 2$), or any of the 3 in compound heterozygous state ($n = 2$).[3,21,23] Patients with all other (combinations of) pathogenic *AGXT* variants were arbitrarily termed B6−, including compound heterozygous patients with a mutation correlated to B6 responsiveness on 1 allele.

Outcome Measures

We evaluated patient survival, event-free survival, and death-censored kidney graft survival. Patients were selected based on their first type of transplant, for example, patients who received CLKT after failure of KT were seen as KT recipients with kidney graft failure. Patient survival was calculated from date of first transplantation to death or censored at last follow-up date. Event-free survival was calculated from date of first transplantation to date of liver graft failure, kidney graft failure, or date of death, whichever came first, or censored at last follow-up date. Liver graft failure was defined as the need for retransplantation or death owing to liver graft failure. Kidney graft failure was defined as the need for retransplantation or resumption of dialysis. Death-censored kidney graft survival was calculated from date of first KT to date of kidney graft failure, censored for death.

Statistical Analysis

Baseline characteristics were compared using χ^2 tests for categorical data and Mann–Whitney *U* tests for not normally distributed numerical data. Cumulative patient and kidney graft survival rates were obtained using life tables. Survival analysis was performed using Kaplan–Meier curves, including log-rank test. Cox regression was used to estimate mortality and graft failure hazard ratios, adjusted for 3 possible confounders (dialysis vintage, age at ESKD, and age at transplantation).

Two types of sensitivity analyses were conducted (see Supplementary Figures), which are as follows: (i) excluding patients with infantile oxalosis, when comparing CLKT with KT or SLKT and (ii) excluding patients with 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		267
- 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 (21.8)	
○ 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 (0.9–26.0)	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.
[a]Genotype was known in 48 of 59 KT recipients.

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

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 ($n = 21$)	Availability (n)	*P* value	CLKT ($n = 99$)	Availability (n)	Isolated KT ($n = 27$)	Availability (n)	*P* value
Sex, *n* (%)		20		21	0.437		99		27	0.166
- Male	11 (55.0)		9 (42.9)			55 (55.6)		19 (70.4)		
- Female	9 (45.0)		12 (57.1)			44 (44.4)		8 (29.6)		
Age at diagnosis, yr, median (IQR)	20.4 (0.3–42.5)	14	30.8 (17.3–40.7)	20	0.124	5.6 (0.5–13.6)	82	26.1 (5.9–44.8)	23	0.002
Infantile oxalosis, *n* (%)	4 (22.2)	18	0	20	0.026	24 (25.8)	93	3 (12.0)[a]	25	0.145
Age at ESKD, yr, median (IQR)	20.3 (0.3–45.7)	16	31.3 (17.2–48.1)	20	0.135	14.9 (0.6–21.0)	78	28.4 (9.5–49.1)	22	0.101
ESKD at time of diagnosis, *n* (%)	14 (77.8)	18	16 (80)	20	0.867	46 (53.5)	86	18 (75.0)	24	0.059
Systemic oxalosis at time of diagnosis, *n* (%)	0	3	4 (40)	10	0.188	5 (15.6)	32	3 (50.0)	6	0.058
Dialysis vintage, yr, median (IQR)	1.4 (0.8–2.6)	9	3.5 (1.9–4.0)	15	0.040	1.2 (0.6–1.9)	66	1.2 (0.9–7.8)	12	0.166
Age at transplantation, yr, median (IQR)	21.0 (2.9–48.8)	14	34.8 (22.4–51.7)	16	0.034	15.4 (3.3–23.0)	92	33.6 (13.7–51.0)	20	0.003
Period of transplantation, *n* (%)		14		16	0.207		93		22	0.028
- Before 2000	3 (21.4)		8 (50)			29 (31.2)		13 (59.1)		
- Between 2000 and 2010	5 (35.7)		5 (31.3)			35 (37.6)		7 (31.8)		
- After 2010	6 (42.9)		3 (18.8)			29 (31.2)		2 (9.1)		
Follow-up period, yr, median (IQR)	7.4 (6.0–10.7)	20	10.2 (4.2–26.3)	21	0.085	5.9 (0.5–11.1)	99	12.5 (10.0–15.6)	27	0.052

CLKT, combined liver kidney transplantation; ESKD, end-stage kidney disease; IQR, interquartile range; KT, kidney transplantation; PH1, primary hyperoxaluria type 1.
[a]These patients were on dialysis for a few years before KT and received CLKT after failed KT.

first transplantation was 16.8 (IQR: 3.9–28.9) years. Data from 244 patients were used for comparative analyses; patients with an isolated PLT were not included ($n = 12$), neither were isolated kidney recipients with unknown genotype ($n = 11$).

Outcomes of CLKT Versus KT According to B6 Responsivity

A total of 207 patients underwent either CLKT or KT, of whom 41 patients (18.9%) were diagnosed with having B6+ *AGXT* genotypes (21 KT and 20 CLKT; Table 2, Supplementary Table S4).

Unadjusted patient survival was similar between CLKT and KT for both B6+ and B6− patients, despite an initial drop in survival after CLKT (Figure 1a and b). Only for B6+ patients, mortality was lower after KT as compared with after CLKT, after adjusting for confounders (adjusted hazard ratio 0.07, 95% CI: 0.01–0.75, $P = 0.028$; Supplementary Table S1). In B6− patients, event-free survival after CLKT was significantly higher than after KT ($P < 0.001$; Figure 1d). Nevertheless, in B6+ patients, event-free survival rates of CLKT and KT were comparable ($P = 0.411$; Figure 1c). Evaluating death-censored kidney graft survival, CLKT yielded significantly better results than KT in both B6− and B6+ patients ($P < 0.001$ and $P = 0.032$, respectively, Figure 1e and f). Yet, life table analyses revealed that the median survival time of the kidney graft in isolated kidney recipients was remarkably longer in B6+ patients as compared with B6− patients (6.9 years and 0.8 year, respectively). Furthermore, after adjusting for dialysis vintage, age at ESKD, and age of transplantation, death-censored kidney graft survival in B6+ patients no longer favored CLKT (Supplementary Table S1). After excluding patients with infantile oxalosis, we observed similar results (Supplementary Figure S1). There were 3 patients, who had developed ESKD in their first year of life, who received an isolated KT. They experienced kidney graft failure after 29 days, 77 days, and 8 years.

Outcomes of CLKT Versus SLKT

Table 3 reveals the baseline characteristics of patients with PH1 who underwent CLKT or SLKT. Patients with SLKT were significantly younger at the time of diagnosis, ESKD, and transplantation as compared with patients who underwent CLKT. Furthermore, patients who underwent SLKT received a liver transplant after 2000 in all but 2 cases, whereas CLKT was performed before 2000 in 35% of the cases. No differences were observed in patient survival, event-free survival, nor death-censored kidney graft survival between CLKT and SLKT (Figure 2a–c, Supplementary Table S5). This remained true after excluding patients with infantile

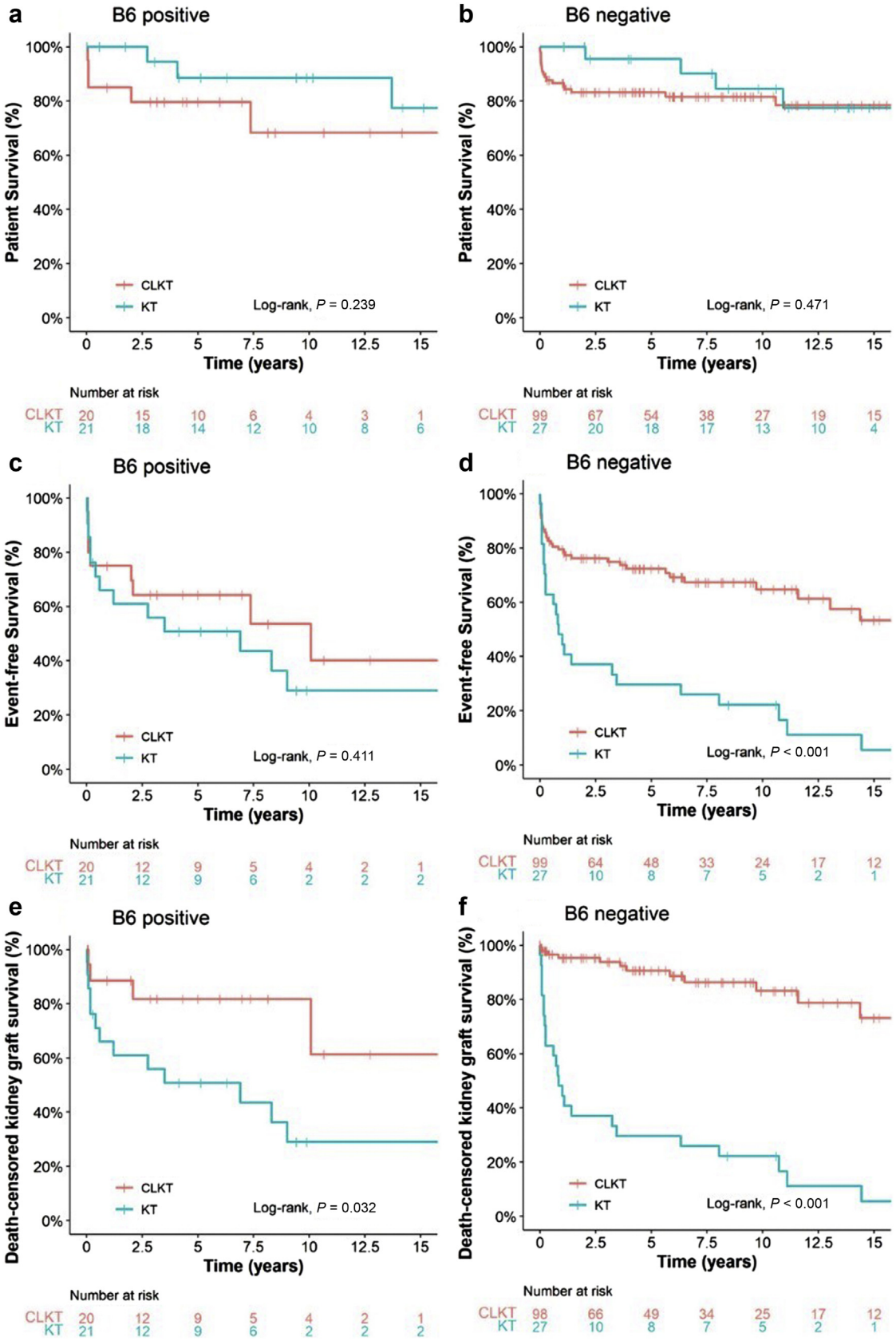

Figure 1. Kaplan–Meier survival analyses comparing CLKT with KT in patients with PH1 with B6+ and B6− mutations. CLKT, combined liver–kidney transplantation; KT, kidney transplantation; PH1, primary hyperoxaluria type 1. (a,b) Patient survival; (c,d) event-free survival; and (e,f) death-censored kidney graft survival.

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Table 3. Characteristics of patients with PH1 who underwent SLKT or CLKT

Characteristics	CLKT ($n = 159$)	Availability (n)	SLKT ($n = 37$)[a]	Availability (n)	P value
Sex, n (%)		159		37	0.526
- Male	86 (54.1)		18 (48.6)		
- Female	74 (47.1)		19 (51.4)		
Genotype, n (%)		119		36	0.941
- B6 responsive	7 (5.9)		2 (5.6)		
- B6 unresponsive	112 (94.1)		34 (94.4)		
Age at diagnosis, yr, median (IQR)	5.8 (0.5–15.0)	124	0.8 (0.4–7.4)	22	0.003
Infantile oxalosis, n (%)	35 (23.6)	148	17 (47.2)	36	0.005
Age at ESKD, yr, median (IQR)	13.6 (0.6–20.5)	121	0.6 (0.3–15.6)	25	0.001
ESKD at time of diagnosis, n (%)	83 (58.5)	142	22 (73.3)	30	0.129
Systemic oxalosis at time of diagnosis, n (%)	6 (14.0)	43	7 (35.0)	20	0.055
Dialysis vintage, yr, median (IQR)	1.2 (0.6–1.9)	97	1.2 (0.8–2.1)	18	0.476
Time between liver and kidney transplant, yr, median (IQR)			1.0 (0.6–1.3)	26	
Age at transplantation, yr, median (IQR)	14.8 (3.3–21.9)	142	3.4 (1.3–16.9)	35	0.094
Period of transplantation, n (%)		144		35	<0.001
- Before 2000	50 (34.7)		2 (5.7)		
- Between 2000 and 2010	53 (36.8)		11 (31.4)		
- After 2010	41(28.5)		22 (62.9)		
Follow-up, yr, median (IQR)	6.4 (1.5–11.5)	159	2.9 (0.8–8.3)	37	0.237

CLKT, combined liver–kidney transplantation; ESKD, end-stage kidney disease; IQR, interquartile range; PH1, primary hyperoxaluria type 1; SLKT, sequential liver–kidney transplantation.
[a]Of 37 patients who were scheduled for SLKT, 26 received both a liver and a kidney transplant.

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

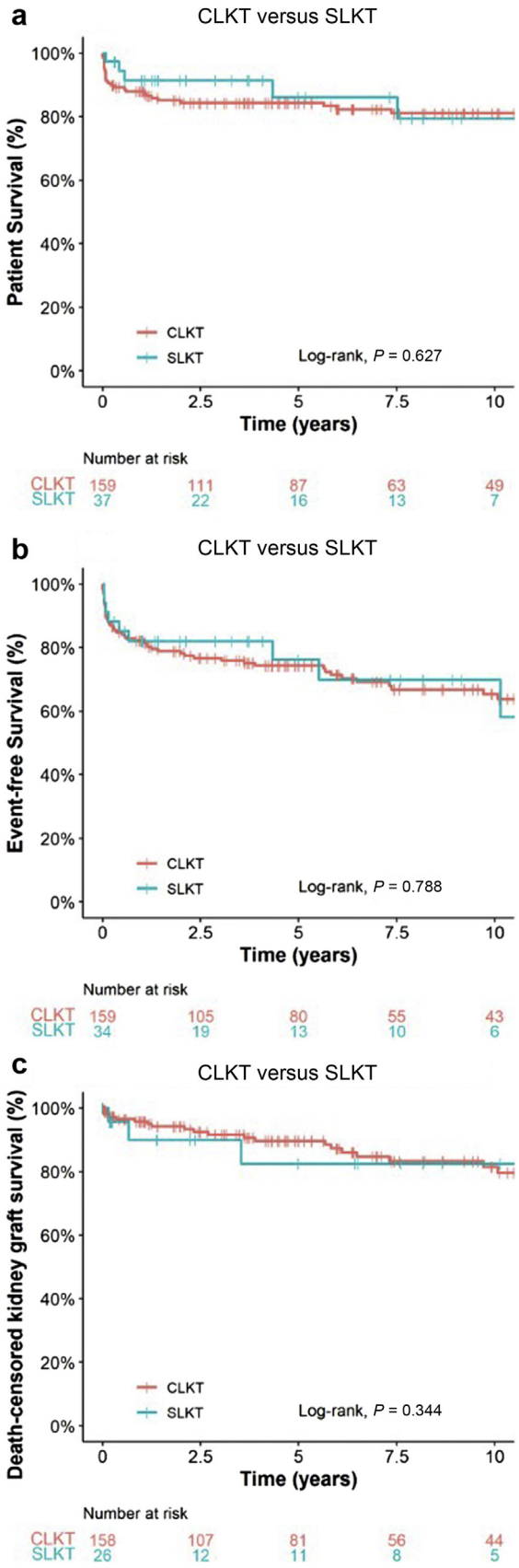

Figure 2. Kaplan–Meier survival analyses comparing CLKT with SLKT. CLKT, combined liver–kidney transplantation; SLKT, sequential liver–kidney transplantation. (a) Patient survival; (b) event-free survival; and (c) death-censored kidney graft survival.

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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.[24,25] 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.[26] Lorenz *et al.*[20] 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.*[20] 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.*[14] 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.*[14] 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.[12,13] 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,[27] though successful combined procedures have been described in 14 children with PH1, including 8 infants who weighed <15 kg at the time of CLKT.[28] 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.[12] In contrast, one could also argue that a functional kidney transplant removes the excessive amount of oxalate more effectively than chronic dialysis treatment,

despite extensive dialysis regimens.[29] The number of patients with systemic oxalosis in our cohort was too small to draw conclusions on the merits of SLKT as compared with CLKT in this group. Third, the availability of donor organs must be considered. In a combined procedure, both organs are harvested from the same deceased donor. In countries where deceased donor organs are in short supply, a sequential procedure may be the only option and may allow for consideration of living related donation. Both SLKT with a single living donor[30] and 2 separate donors[31] have been described in patients with PH1. The first option holds an immunologic advantage, but donor risks should also be taken into consideration.[29] On the basis of our data, the simultaneous and the sequential approach seem to be equally effective, and the choice should therefore be based on the clinical characteristics of the patient and the availability of donor organs.

Pre-Emptive Liver Transplantation

Brinkert *et al*.[32] 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.[26] 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[33] 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.[34] Though very few cases with atypical *AGXT* genotypes may respond to B6 treatment,[35,36] we classified patients based on the most common pathogenic variants of which genotype-phenotype correlations are better established. Our data confirm the assumption that patients with B6+ genotypes did indeed not benefit from the oxalate-reducing effect of liver transplantation in contrast to patients with B6− genotypes. More reliable methods to confirm clinical B6 response are under development but require validation in a larger patient cohort.[37] Ideally, future research should focus on obtaining more insight into possible predictive factors of outcome, including *AGXT* genotype, plasma oxalate, and glycolate values, and manifestations of systemic oxalosis to further individualize and improve therapeutic strategies for patients with PH1.

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.[7,38] These promising drugs will modify therapeutic management of patients with PH1 and hopefully preclude the need for liver transplantation in the near future.[39] 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.[7,39] 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

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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.

Figure S1. Kaplan–Meier survival analyses comparing CLKT with KT in patients with PH1 selected on B6 responsiveness; cases with infantile oxalosis were excluded.

Figure S2. Kaplan–Meier survival analyses, comparing CLKT with SLKT in patients with PH1; cases with infantile oxalosis were excluded.

Figure S3. Kaplan–Meier survival analyses comparing CLKT with SLKT in patients with PH1; transplantations were performed after January 1, 2000.

Figure S4. Kaplan–Meier survival analyses comparing CLKT with SLKT in patients with PH1; transplantations were performed after January 1, 2010.

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