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# New Insights Regarding Organ Transplantation in Primary Hyperoxaluria Type 1



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See Clinical Research on Page 210

One of the primary challenges in rare diseases is the lack of high-quality evidence to guide decision-making. Contributing factors include the small number of affected patients who are often widely dispersed across many medical centers, the relatively small number of physician/scientist experts in a given rare disease and conversely the lack of expertise in the general medical community, and the relatively limited resources for study of diseases that affect relatively few people. The choice of an optimal transplantation approach for patients with primary hyperoxaluria type 1 (PH1) is a perfect example of such a clinical question.[1]

Unfortunately, kidney failure is a frequent outcome in PH1 (Figure 1). Given the risk of recurrent oxalate nephropathy, liver transplantation is often performed to correct the underlying metabolic defect. Nevertheless, the correct approach, combined liver/kidney transplant (CLKT), sequential liver/kidney transplant (KT), KT alone, and preemptive liver transplant, has been the subject of much debate. Because of the limited published data, these debates have often been based on anecdotal experience and local preference. Although a gold standard randomized, controlled study to determine the superiority of any one modality will not likely ever be performed, the field benefits from the study published here in the *KI Reports* by Metry *et al.*,[2] which reports a large retrospective European experience since 1978 for organ transplantation in PH1.

The authors extracted data from 267 patients with PH1 in the OxalEurope PH registry who underwent liver and/or kidney transplantation between 1978 and 2019. The 211 with available genetic testing results were subclassified into those homozygous for likely vitamin B6-responsive (B6+; $n = 46$) versus nonresponsive (B6−; $n = 165$) mutations.[3] Patient outcomes after CLKT, KT, sequential liver/KT, or preemptive liver transplant were then evaluated, including patient survival, event-free survival, and kidney graft survival.

An important observation was that any form of liver transplant—sequential liver/KT, CLKT, or preemptive liver transplant—carried significant short-term mortality that approached 20%. Furthermore, outcomes were similar between sequential liver/KT and CLKT. Thus, these data suggest that the choice between a combined versus sequential transplant strategy can be individualized based on center experience and individual patient circumstances. Nevertheless, the short-term risk of preemptive liver transplant suggests that this is not a preferred approach and that any transplant should be deferred until patients have approached or reached kidney failure.

The choice between a CLKT versus KT alone seems more nuanced based on this data set and analysis. For patients who were B6−, the CLKT imparted important patient survival and event-free survival advantages. Thus, this study supports an approach that replaces both liver and kidney in patients with B6−. Nevertheless, among the B6+ group, the data were more mixed. Patient survival in analyses that adjusted for comorbidities was slightly better for patients with B6+ who received a KT alone, even though death-censored kidney graft survival was better in the patients with CLKT. These data suggest that if a KT alone is pursued in patients with B6+ PH1, they may require multiple KTs over time. This may account for the similar event-free survival between patients with B6+ who underwent

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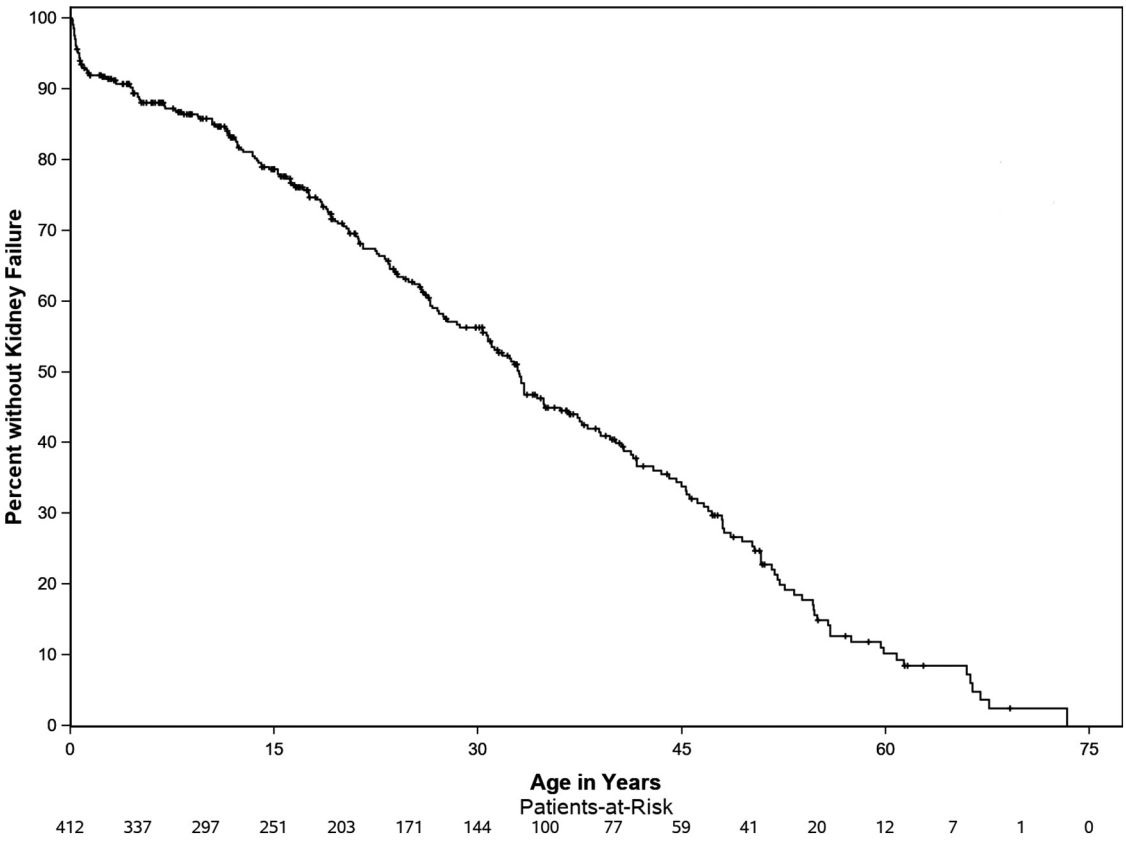


**Figure 1.** Kidney survival in PH1. Among 412 patients with PH1 without kidney failure on enrollment in the Oxalosis and Hyperoxaluria Rare Kidney Stone Consortium PH registry to 2021, approximately 50% had kidney failure by age 30 years and 90% by age 60 years. PH1, primary hyperoxaluria type 1.

KT versus CLKT procedures. Thus, this paper adds to previous reports which suggest that KT alone is a viable option in patients with B6+.

It is important to recognize that B6 responsiveness was inferred from genotype and not actual biochemical response. This is entirely reasonable, especially because sequential measures of urinary oxalate excretion can be challenging, even in patients with intact kidney function, and is not possible in patients who have advanced chronic kidney disease or kidney failure. Nevertheless, it is not certain that all patients homozygous for specific mutations thought to be B6+, even the most common G170R mutation, will experience equal reductions in oxalate generation on vitamin B6.[4] There can also be important issues with tolerance, compliance, or other yet-to-be-understood features that could affect the degree of B6 response. This paper also did not address the subset of patients heterozygous for a mutation thought to be B6 responsive.[5]

Even with these caveats, this publication provides important information from a large cohort of patients with PH1 at a critical time when novel treatments are emerging for PH1. A small RNA interference therapy against hepatic glycolate oxidase (lumasiran) was recently found to effectively reduce urinary oxalate excretion in a short-term study[6] and has been approved in both Europe and the United States for clinical use.[7] A second RNA interference that targets hepatic lactate dehydrogenase A (nedosiran) is currently completing phase 3 clinical studies.[8] These novel therapies have been developed to reduce endogenous oxalate production through interference with critical enzymes along the oxalate metabolic pathway. Viewed considering the significant short-term mortality for hepatic transplantation, and if these medications are as safe and effective as we hope, they could drastically improve short- and long-term outcomes in this rare disease population, especially if introduced long before chronic kidney disease occurs.[9] The relatively good outcomes in the B6+ KT alone group suggest that all patients with PH1 who respond to an RNA interference and have kidney failure might eventually avoid a liver transplant and could instead receive a KT alone. Nevertheless, we do not yet have data to know whether all patients respond

equally to lumasiran (or possibly nedosiran), and whether the outcomes would mirror those of the patients with B6+. Thus, this paper provides valuable baseline data that will be useful for future investigations in the efficacy of novel therapies. Finally, the benefit of RNA interference versus B6 in the B6+ group in any long-term side effects remains to be determined.

Overall, this report highlights the importance of well-maintained registries for rare disease research. Only through organized and collaborative collection of laboratory and clinical data can we provide natural history data to inform the planning and interpretation of well-designed clinical trials that evaluate the novel therapies desperately needed for so many rare and orphan diseases. These data also provide important benchmarks for the outcome of patients once on treatments. We appreciate the authors' dedication to their patients and colleagues, illustrated through this important data analysis and presentation.

## DISCLOSURE

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