Liver Transplantation in Primary Hyperoxaluria Type 1: We Have to Find an Alternative!

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Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disease caused by the functional defect of hepatic alanine-glyoxylate aminotransferase (AGT), resulting in the overproduction of oxalate (Figure 1). It leads to early end-stage renal disease (ESRD) in most patients.[1] To date, the only way to cure PH1 patients with ESRD is dual liver-kidney transplantation.

A 16-year-old anuric PH1 Algerian boy, on dialysis since 4 years, traveled to our center for sequential liver-kidney transplantation. Because of the presumed systemic oxalosis, the sequential approach was decided. He received an LT from his uncle in June 2020. The posttransplant course was complicated with infections, recurrent biliary strictures, encephalopathy, and persistent liver dysfunction. Two months of hospitalization in the intensive care unit led to severe malnutrition, sarcopenia, psychologic stress, and to unaffordable expenses for his parents. The patient is currently hemodialyzed in our center with a worrying medical condition.

In addition to the organ access issue,[2] LT is associated with nonnegligible morbidity and mortality. The European PH1 transplant registry experience reported 1-, 5-, and 10-year patient survival rates of 86%, 80%, and 69%, respectively.[3] These results are not optimal. While LT was ethically justified until now—being the only way to cure the metabolic defect—it will no longer be the case in the near future. Indeed, innovative drugs are currently in the pipeline to treat hepatic metabolic defect.

Preliminary results of Illuminate-A trial, a phase 3 trial that evaluates lumasiran (an RNA interference [RNAi] drug targeting glycolate oxidase; Figure 1) in PH1 patients with estimated glomerular filtration rate >30 mL/min, showed a dramatic decrease of urine oxalate levels at 6

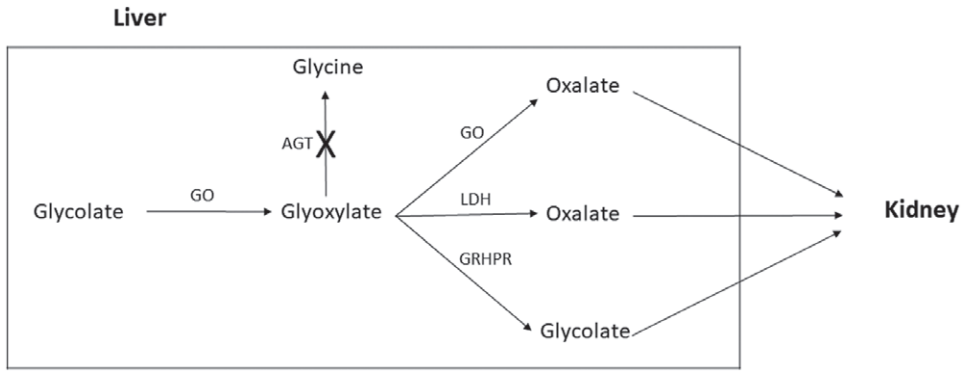

FIGURE 1. Glyoxylate metabolism in the hepatocyte in primary hyperoxaluria type I. In the peroxisome of normal hepatocyte, GO catalyzes the conversion of glycolate to glyoxylate. Then AGT catalyzes the conversion of glyoxylate to glycine. In primary hyperoxaluria type 1, glyoxylate accumulates as a result of AGT deficiency and is converted to oxalate by hepatic LDH and GO and to glycolate by GRHPR. Oxalate and glycolate are finally eliminated from the body by the kidneys. AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; GRHPR, glyoxylate reductase-hydroxypyruvate reductase; LDH, lactate dehydrogenase.

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months without important side effects.[4] Currently, a phase 3 trial—Illuminate-C trial—is recruiting to evaluate the efficacy of lumasiran in PH1 patients with an estimated glomerular filtration rate of ≤45 mL/min, including chronic dialyzed patients (NCT04152200). If conclusive, it opens the possibility to consider treating PH1 patients with ESRD by combining this medication and kidney transplantation. Other drugs are currently tested in clinical trials, including oral administration of Oxabact (an anaerobic bacteria that uses oxalate as the sole source of energy), nedosiran (an RNAi drug targeting hepatic *LDHA*; NCT04042402; Figure 1), and stiripentol (an antiepileptic drug inhibiting LDH; NCT03819647; Figure 1).[5] Allogenic hepatocyte transplantation has been unsuccessful until now, mostly because the number of engrafted hepatocytes required for clinical recovery can hardly be technically provided.[5] Delivery of normal *AGXT* gene (coding for AGT) through different vectors is also in preclinical development.[5]

With RNAi drugs, it is likely that LT will disappear from transplantation strategies in the near future, thereby improving patient survival and quality of life. Importantly, it can be anticipated that the cost of these drugs will be unaffordable for some healthcare systems from emerging countries, where PH1 is more prevalent.[1] The Transplant Community should be unified in asking pharmaceutical companies a solidarity strategy to include emerging countries in ongoing trials and drug supply when they will be available.

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