Journal of Liver Transplantation 2 (2021) 100017

Contents lists available at ScienceDirect

Journal of Liver Transplantation

journal homepage: www.elsevier.com

Editorial

Management of primary hyperoxaluria type 1: Does liver transplantation still have a future?

ARTICLE INFO

Article history:
Received 2 June 2021
Accepted 2 June 2021
Available online xxx

Keywords:
Primary hyperoxaluria type 1- liver transplantation-RNA interference drugs

In this issue, Alkhunaizi et al. report two cases of early oxalate nephropathy recurrence leading to early graft loss after dual liver-kidney transplantation in two siblings in end-stage kidney disease (ESKD) secondary to primary hyperoxaluria type 1 (PH1). This paper highlights the complexity of the transplant management of PH1 patients.

PH1 is a rare autosomal recessive disease caused by the functional defect of the liver-specific alanine-glyoxylate aminotransferase (AGT) that catalyzes the transamination of glyoxylate to glycine. It results in an accumulation of glyoxylate leading to an excessive production of both oxalate and glycolate (Fig. 1) [1]. The massive amount of oxalate produced is excreted by the kidney in the form of insoluble calcium salt, leading to kidney stone formation, nephrocalcinosis and progressive decline of kidney function. When estimated glomerular filtration rate (eGFR) drops to 30–45 mL/min/1.73 m^2 of body surface area (BSA), the kidney becomes unable to excrete all the oxalate it receives, resulting in an increase in plasma oxalate (POx) levels and ultimately in a systemic accumulation in nearly all organs, especially the bones. As illustrated in the paper by Alkhunaizi et al., if this systemic storage is not managed efficiently-or ignored- before kidney transplantation (KT), it can rush into the newly-implanted kidney graft and potentially lead to irreversible early allograft damages.

Conservative measures-including massive fluid intake, pyridoxine, calcium oxalate crystallization inhibitors-have proven their efficacy to slow down the deterioration of kidney function and should be apply as soon as PH1 is diagnosed [1]. Despite this, the majority of patients reach ESKD in the three first decades of life. Moreover, some patients are diagnosed with PH1 while already in ESKD [1]. As AGT is a liver specific enzyme, liver transplantation (LT) is the only way-until now- to cure the metabolic defect. Consequently, current KT strategies for the management of PH1 patients in ESKD nearly always include LT, either at the same time (combined LKT) or before KT (sequential LKT) [1]. The sequential approach is proposed by some centers in PH1 patients already on chronic dialysis-in whom oxalate systemic storage is supposedly high- to allow a dialysis period after LT that will decrease the oxalate storage. Some centers also propose isolated KT in highly selected patients who showed relatively slow evolution of the disease and who demonstrated Vitamine B6 sensitivity [2]. However, this approach remains controversial.

Liver transplantation is the main issue of the current transplant strategies. It delays access to transplantation regarding the worldwide organ shortage. Moreover, it is associated with morbidity and mortality that should not be minimized, especially in such a young population [3]. Jamieson et al. reported the European PH1 transplant registry experience from 1984 to 2004 showing patient survival rates of only 86%, 80% and 69% at 1-, 5- and 10- year respectively. While LT was justified-being the only way to restore normal AGT activity- it might not be the case anymore considering the emerging therapies in the pipeline [4,5].

To reduce oxalate production in PH1 patients, RNA interference (RNAi) drugs knocking down key enzymes involved in hepatic oxalate synthesis have been developed. (RNAi) drugs target the endogenous mRNA transcript of a given gene, leading to its cleavage and subsequently the suppression of the encoded protein. Lumasiran is an RNAi drug targeting hepatic glycolate oxidase (GO), a key enzyme in oxalate synthesis catalyzing the oxidation of glycolate to glyoxylate, the immediate precursor to hepatic oxalate synthesis (Fig. 1). Six months results of Illuminate A trial (including PH1 patients ≥6 years with eGFR≥30 mL/min/1.73 m^2 BSA) were recently published and showed excellent efficacy to decrease urine oxalate levels (UOx) without important side effects [6]. Illuminate B (PH1 patients ≤5 years with preserved kidney function, NCT03905694) and Illuminate C (all age, eGFR ≤45 mL/min/1.73 m^2 BSA, including patients on dialysis, NCT04152200) are ongoing. Lumasiran is administered subcutaneously, and was recently approved by both the US Federal Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of adult and pediatric patients with PH1 [7,8]. Nedosiran is another RNAi drug targeting LDH that is responsible for the final conversion of glycoxylate to oxalate (Fig. 1). A phase III clinical trial (PH1 ≥ 6 years, eGFR≥30 mL/min/ 1.73 m^2 BSA, NCT04042402) is ongoing.

With this fascinating advance in treatment brought by RNAi drugs, management of PH1 patients with ESKD should be adapted. Indeed, if efficacy and safety of these molecules in patients with kidney impairment -including patients on dialysis- is assessed, LT will no longer be part of the treatment. We recently proposed new strategies of management for PH1 patients with the use RNAi drugs [5]. We suggested initiating RNAi treatment-on top of conservative measures- in all patients diagnosed with PH1. In patients with chronic kidney disease (CKD) stage 4–5, early KT could be proposed in patients without evident systemic oxalosis. In patients on dialysis and/or

https://doi.org/10.1016/j.liver.2021.100017

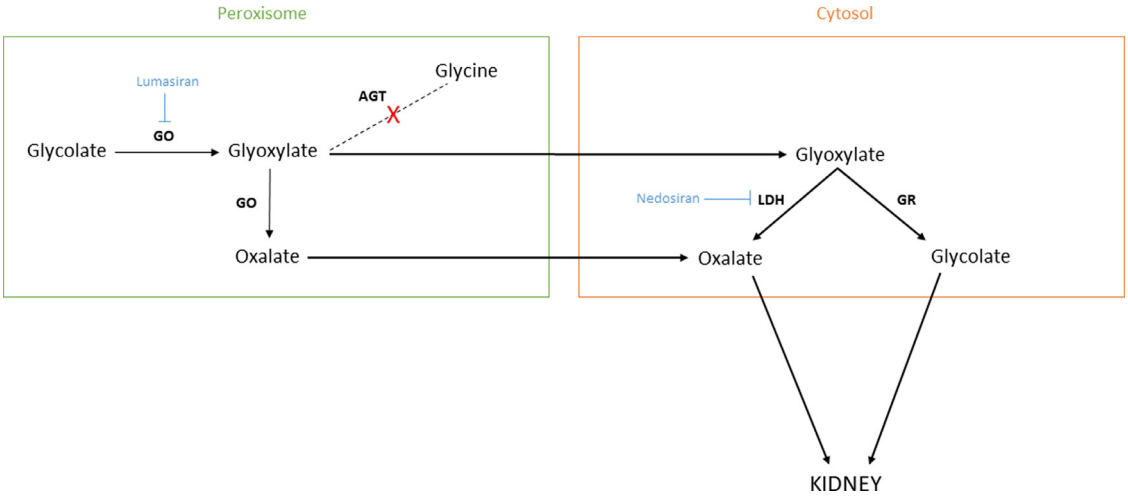

Fig. 1. Glyoxylate metabolism in the hepatocyte in primary hyperoxaluria type I. In the peroxisome of normal hepatocyte, glycolate oxidase (GO) catalyzes the conversion of glycolate to glyoxylate. Then alanine-glyoxylate aminotransferase (AGT) catalyzes the conversion of glyoxylate and alanine to glycine and pyruvate and of serine to hydroxypyruvate. In primary hyperoxaluria type 1, 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 (GR). Oxalate and glycolate are eliminated from the body by the kidneys. Lumasiran and Nedosiran target GO and LDH, respectively.

CKD4−5 with systemic oxalosis, hemodialysis should be initiated to decrease POx value ≤20 μmol/L, before allowing KT. This strategy needs to be validated.

Regarding these important medical advances, many questions remain to be answered. The optimal timing for KT after the correction of the metabolic defect is one of the most challenging question. Indeed, it would be logical to perform KT when the level of systemic storage is low to limit the risk of oxalate precipitation in the graft. However, in clinical practice, it is very difficult to estimate the systemic storage correctly. Most teams currently use POx as an estimate of systemic oxalosis and consider KT when POx is <20 μmol/L. However, POx is an imperfect reflection of systemic oxalosis that does not assess the real potential for oxalate release from bones. Developing tools to evaluate the systemic oxalate burden will help delineate the best timing for KT to avoid oxalate recurrence in the kidney allograft. The optimal management of patients after KT is also an important question. Some teams systematically use hemodialysis during a defined period, others monitor POx and apply hemodialysis until levels fall under 20 μmol/L, and others limit hemodialysis to patients with significant systemic oxalate involvement when urine excretion is limited and for patients with acute tubular necrosis or delayed graft function. However, the benefit of one option on another is unknown. It is also important to remind that after combined LKT, UOx remains elevated for years after correction of the metabolic defect [9]. Consequently, conservative measures should be maintained after KT until normalization of UOx to protect the newly transplanted kidney from oxalate deposition. Questions regarding these new treatments and the outcome of kidney allograft, interactions with immunosuppressive drugs and long-term complications will also have to be rapidly answered.

Finally, there is no doubt that these innovative treatments will be unaffordable for some emerging countries where the disease is more prevalent [1]. In these countries, LT might still be the only option. However, the Transplant Community should pay attention and make action to ensure that these patients will not be excluded from RNAi therapies.

In conclusion, the management of PH1 patients with ESKD will undoubtedly be modified in the near future. It is likely that LT will no longer be necessary to treat the metabolic defect associated with PH1, contributing hopefully to improve patients' survival and quality of life. Some questions remain to be answered before clinical application.

Fundings

None.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Arnaud Devresse declares consult fees for Alnylam Pharmaceuticals.

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