Lessons for the clinical nephrologist: Lumasiran as the future Cornerstone Treatment for Patients with Primary Hyperoxaluria type 1?

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Primary hyperoxaluria type 1 (PH1) -OMIM #259900- is a rare recessive autosomal disorder caused by a deficiency of the liver peroxisomal enzyme alanine-glyoxylate-aminotransferase (AGT), which catalyzes the conversion of glyoxylate to glycine. Reduced AGT activity leads to the conversion of glyoxylate to oxalate (Figure 1). Oxalate forms insoluble calcium oxalate crystals that accumulate in the kidney and ~~further~~ subsequently in other organs- when the kidneys are saturated- leading to systemic oxalosis.[1] The most severe PH1 cases start during the first months of life with a rapid development of ~~and may manifest themselves straightaway by~~ kidney failure.[1] Before 2020, treatment of PH1 ~~was only based~~mainly relied on supportive measures including intensive water intake, and on the prescription of vitamin B6 and oral crystallization inhibitors. Despite this, many patients ~~continue to~~ still experience serious and life-threatening ~~-~~complications especially end-stage kidney disease.[1] To date, ~~the only way to cure~~ PH1 patients with kidney failure ~~is~~ can only be cured by dual liver-kidney transplantation with ~~an~~ the well-known increased morbidity and mortality risks ~~of morbidity and mortality~~.[2]

The following two cases describe the outcomes of two PH1 patients treated with lumasiran-a new innovative ~~treatment for PH1~~therapeutic approach.

Case 1

Patient 1 born in October 2012 was fortuitously diagnosed ~~fortuitly~~ with bilateral nephrocalcinosis just after birth. ~~The child~~She had both elevated urinary oxalate/creatinine ratio (Uox/creat) at 896 (~~normal ranges~~NV for infant <6 months ~~of age~~: 320) mmol/mol (700 mg/g creatinine) and elevated glycolic acid/creatinine ratio at 2744 (~~normal value~~NV <200) mmol/mol (1829 mg/g). Kidney function was normal. The diagnosis of PH1 was confirmed by genetic testing with compound heterozygous pathogenic variants c.568G>A (p.Pro11Leu) and c.121G>A (p.Gly41Arg) in *AGXT* gene. A gastrostomy tube was inserted for hyperhydration together with oral treatment consisting of potassium citrate and pyridoxine. In June 2013, the nephrocalcinosis was undetectable on ultrasound despite persistent elevated oxaluria at 855 mmol/mol (667 mg/g). In February 2020, kidney ultrasound showed ~~the presence of~~formation of bilateral kidney stones, ~~that were~~ absent in ~~a~~the previous ultrasound performed two years ~~prior~~earlier~~not present in 2018~~. In July 2020, she started lumasiran through a compassionate use ~~from October 2020 together with~~in addition of the usual conservative measures with hyperhydration, pyridoxine and potassium citrate. Tolerance of lumasiran has been excellent. The mean value of Uox/creat reached 158 (~~normal range~~NV for age < 70) mmol/mol (123 mg/g) between January 2018 and July 2020 (figure 2) before lumasiran ~~was started~~onset, decreasing ~~and t~~ thereafter ~~decreased~~ to 108 mmol/mol (84 mg/g) from July 2020 up to now, representing a ~~drop of~~ 31% drop (Figure 2A). Moreover~~In the meanwhile~~, lumasiran allowed a reduction in hyperhydration ~~could be reduced since February 2021~~ from 3.5 ~~L/day down~~ to 2 L/day, ~~starting~~ from February 2021 onwards ; ~~and soon will allow~~ the gastrostomy's tube will soon be removed ~~removal~~ ~~alongside~~together with the suspension of ~~a~~the specialized nurse's visits ~~allowing to interrupt~~

~~the visit of a nurse~~ at school~~. to use the gastrostomy that will be removed soon~~. She is still being treated with lumasiran.

Case 2

Patient 2 born in March 2021 from consanguineous parents was diagnosed with PH1 in May 2021 ~~(~~after bilateral nephrocalcinosis ~~)~~discovery. The child had an elevated UOx/creat at 1626 (NR for age < 320) mmol/mol (1270 mg/g). ~~The diagnosis of~~ PH1 diagnosis was confirmed with a homozygous pathogenic variant (c.33dup) of *AGXT* gene. ~~The c~~Conservative treatment was ~~initiated combining~~initiated combining hyperhydration, potassium citrate and pyridoxine. Lumasiran was ~~initiated~~ started through a compassionate use in July 2021. Urinary oxalate/creatinine ratios lowered to 1043 mmol/mol (814 mg/g), 844 mmol/mol (659~~63.5~~ mg/g), 389 mmol/mol (303 mg/g), and 288 mmol/mol (225 mg/g) at day 15, day 30, month 2, and month 5 after treatment ~~initiation~~onset, respectively (figure 2B). ~~Tolerance of l~~Lumasiran tolerance has been excellent and kidney function has remained normal~~,~~ so far. Nephrocalcinosis was stable at month 8. A naso-gastric tube was inserted at~~in the beginning of the~~ treatment initiation to ensure ~~important~~ hyperhydration and then removed when urinary oxalate dropped ~~and hyperhydration reduced~~. To date, the patient has a normal growth and she shows a small developmental ~~delay~~ retardation with global hypotonia and delayed sitting ~~treated by postural physiotherapy~~ability. She is still being treated with lumasiran.

Lessons for the clinical nephrologist

RNA interference (RNAi) is a natural defense mechanism ~~for~~ against ~~the~~ invasion of exogenous genes mediated by small interfering RNAs[2]. Synthetic small interference RNA with a specific selected sequence can be designed to pair with endogenous mRNA of a targeted gene leading to its cleavage and ~~the~~ subsequent silencing of the encoded protein. RNAi is a quite selective process ~~but there is~~with a theoretical ~~probability~~ possibility of off-target effects in which an unrelated gene similar to the target gene can also be silenced[3]. However, ~~at this time,~~ there is~~are~~ no clinical evidence of ~~these~~ such off-target effects in ~~the~~ clinical trials so far [4-7]. Lumasiran is a subcutaneously administered, liver-directed RNA interference therapy targeting the messenger RNA of glycolate oxidase ~~and~~ subsequently reducing hepatic oxalate production (figure 1). Both ~~S~~safety and efficacy of lumasiran ~~wereas~~ have been assessed in clinical trials ~~three clinical trials~~ (Table 1)[4-7], allowing its approval by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) on November 2020. Hopefully, ~~especially if administrated early in the course of the disease,~~ lumasiran will improve the current dramatic kidney outcome of PH1 patients, especially if administrated early in the course of the disease~~despite conservative treatments~~.[1] In addition, it is likely that this drug will also improve patients quality of life ~~of patients~~ as illustrated by our cases. Indeed, ~~our~~ the first patient ~~was~~ had been treated for 8 years with an aggressive conservative therapy ~~during 8 years with~~including a gastrostomy, ~~implying~~ and therefore ~~the visit of~~ a daily nurse visit at school, and ~~some~~ multiple limitations in her everyday life. Thanks to lumasiran started 18 months ago, ~~the~~ water intake has been progressively reduced ~~progressively~~ and the gastrostomy will be soon removed. Lumasiran offered the patient a real improvement in her quality of life. In ~~our~~ the second patient, the

results were even more spectacular in terms of rapid and sustained drop of urinary oxalate levels. The infant has currently a normal everyday life, a normal kidney function and she didn't experienced ~~no~~any side effects of lumasiran, contrasting with the high rate of early kidney failure described in severe infantile forms.[8]

How to use lumasiran?

Lumasiran (3 mg/kg) is administered once monthly for the first three doses, followed by maintenance doses given once every 3 months beginning 1 month after the last loading dose.[4] Lumasiran is given on top of the conservative measures including, hyperhydration, potassium citrate and vitamin B6 (pyridoxin) if sensible. The sooner the treatment is initiated, the better ~~it seems to be~~the outcome as documented by ~~. Indeed,~~ Meaux et al ~~published~~ in a small case-serie of 3 young infants with high oxaluria/creatinin ratios at diagnosis and preserved renal function in 2 ~~patients~~ of them when lumasiran was initiated.[9] Favourable results were achieved in terms ~~of reduction~~ of urinary oxalate levels reduction together with a good clinical tolerance. The effects of lumasiran on nephrocalcinosis were more mitigated ~~though~~, but this has to be balanced with the short (< 1 year) follow-up ~~was~~of those patients~~eitns short (< 1 year)~~. On the basis of their experience, the authors suggested to initiate lumasiran in severe infantile forms as soon as ~~the~~ a biochemically diagnosis is ~~biochemically~~ highly suspected, without waiting for genetic confirmation ~~in these severe infantile forms~~. Similarly, our second patient received lumasiran at a very young age allowing a dramatic decrease in oxaluria at month 5 but also without any effect on nephrocalcinosis so far, suggesting that ~~. Effects on~~ nephrocalcinosis improvement may be delayed ~~and~~ and that a ~~need~~ longer follow-~~-~~up is required to observe an improvement.

Other innovative treatments in the pipeline.

Nedosiran is an RNA interference agent that inhibits hepatic lactate dehydrogenase (LDH), the enzyme responsible for the common, final step of oxalate production (Figure 1). Safety, pharmacokinetics, pharmacodynamics, and exposure-response was recently assessed in a phase I study.[10] Stiripentol, an old safe antiepilelieppetic drug, also inhibits hepatic LDH, but its efficacy was only assessed in vitro, in animal models and in one case report.[11] Other strategies as the use of *Oxalabacter formigenes* (an anaerobic oxalate-degrading bacteria), chaperone molecules or gene therapy are more or less advanced in clinical development.[2]

Unresolved questions.

The dose for an optimized management of PH1 with lumisaran is currently unknown ill-defined ; of note, and the French team[9] had to increase a transiently increase in the administration frequency (? ou dose ?) of up administration to 6 mg/kg/monthly was initiated by Meaux et al[9] in their patient treated just after birth to obtain a deeper reduction in urinary oxalate level. In all published cases, lumasiran was given on top of conservative measures (high water intake, potassium citrate with or without pyridoxine). In our paperthe present report, oxaluria remains substantially increased in both patients while percent reduction in oxalate excretion is much emphasized, it should also be underlined that resultant oxaluria remains substantially increased. It suggesting that the need for additional preventive measures still remain snecessary.

In this context Iit is still unknown if lumasiran might will allow in a long term follow-up to reduceing these measures that with a negative impact on quality of life of PH1 patients (especially for hyperhydration in infants and children) especially for hyperhydration in infants and children. in a long term follow-up. Similarly Likewise it has to be determine wether lumasiran might reduce or delay the use of intensive dialysis regimen often required

in PH1 patients. ~~-that may dramatically affect the quality of life- remains to be demonstrated.~~

~~Moreover,~~The question which now arises is to know whether ~~to assess if~~ lumasiran m~~ay~~ight replace liver transplantation ~~among~~within~~in~~ the transplant strategies ~~for~~ in PH1 patients ~~in~~ with ESKD ~~is sill an another important unresolved need~~. In this context, Joher et al recently published a case of early oxalate nephropathy recurrence ~~of oxalate nephropathy~~ after kidney transplantation in a PH1 patient previously treated with lumasiran~~.~~[12] A precise algori~~y~~thm to ~~d~~differentiate patients who need a combined liver-kidney transplantation from those requiring a renal tranplantation only is urgently required.

Main teaching points.

Lumasiran is a new promising treatment for~~in~~ PH1, providing great hopes in improving the dramatic outcomes of this rare disease. It effectively reduces ~~effectively~~ hepatic oxalate production. We here report optimistic clinical treatment outcomes in one child and one infant followed in our center. In both cases, Lumasiran was associated with reduction in urine oxalate levels, improvement of quality of life, without significant untoward side-effects. Important unresolved questions such as the place for combined liver-kidney transplantation in PH~~K~~1 patients with ESKD must be addressed in a near future.

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Table 1: Summary of the main results of Illuminate trials

Trial	Main inclusion criteria	Main findings
Illuminate-A[3,4]	°Confirmed *AGXT* mutation °≥6 years °eGFR ≥ 30 mL/min/1.73 m^2 Randomized (2:1); 6 months full double-blind, and then 3 months blinded followed by open-label treatment, **n=39**	**Month 6:** 66.9% of mean reduction from baseline of 24 hr UOx. 13% of patients had improvement of nephrocalcinosis grade. **Month 12:** 64.1% of mean reduction from baseline of 24 hr UOx. 46% of patients had improvement of nephrocalcinosis grade. **No major side effect**
Illuminate-B[5]	°Confirmed *AGXT* mutation °<6 years °eGFR ≥ 45 mL/min/1.73 m^2 in patients aged ≥12 months or non-elevated creatinine in patients aged <12 months Open-label single-arm, **n=18**	**Month 6:** 72% of mean reduction from baseline of 24 hr UOx. **No major side effect**
Illuminate-C[6]	°Confirmed *AGXT* mutation °all ages °eGFR ≤ 45 mL/min/1.73 m^2 including patients in chronic dialysis. Open-label single-arm, **n=21**	**Month 6:** **Cohort A-not on dialysis (n=6):** 33.3% of mean reduction from baseline POx Cohort B-on dialysis (n=15): 42.4% of mean reduction from baseline POx **No major side effect.**

Abbreviations: eGFR, estimated glomerular filtration rate; POx, plasma oxalate; UOx, urine ocalate.

Figures legend

Figure 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 (GRHPR). Oxalate and glycolate are finally eliminated from the body by the kidneys. Lumasiran inhibits hepatic GO.

Figure 2: Evolution of urine oxalate level in patient 1 (A) and patient 2 (B).