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Primary hyperoxaluria type 1: novel therapies at a glance

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ABSTRACT

Primary hyperoxaluria type 1 (PH1) is a rare and severe autosomal recessive disease of oxalate metabolism, resulting from a mutation in the *AGXT* gene that encodes the hepatic peroxisomal enzyme alanine–glyoxylate aminotransferase (AGT). Until recently, treatment of PH1 was supportive, consisting of intensive hyperhydration, use of crystallization inhibitors (citrate and neutral phosphorus), in a subset of responsive PH1 patients' pharmacologic doses of vitamin B6 (pyridoxine), and kidney and liver transplantation when patients progressed to kidney failure. Treatment approaches have been similar for PH2 caused by mutations in hepatic glyoxylate reductase/hydroxypyruvate reductase (*GR/HPR*), although pyridoxine does not have any benefit in this group. PH3 is caused by mutations of mitochondrial 4-hydroxy-2-oxoglutarate aldolase (*HOGA1*) and was the most recently described. Kidney failure appears less common in PH3, although kidney stones occur as frequently as in PH1 and PH2. Oxalate metabolism in the liver is complex. Novel therapies based on RNA interference (RNAi) have recently emerged to modulate these pathways, designed to deplete substrate for enzymes upstream and decrease/avoid oxalate production. Two hepatic enzymes have been targeted to date in PH: glycolate oxidase (GO) with lumasiran and lactate dehydrogenase A (LDH-A) with nedosiran. Lumasiran was approved for the treatment of PH1 in 2020 by both the European Medicines Agency and the Food and Drug Administration, whilst clinical trials with nedosiran are ongoing. Results with the two RNAi therapies demonstrate a significant reduction of urinary oxalate excretion in PH1 patients, but long-term data on efficacy (preservation of kidney function, decreased stone events) and safety remain to be established. Nevertheless, the hepatically targeted RNAi approach represents a potential 'game changer' in the field of PH1, bringing hope to families and patients that they may be able to avoid liver and/or kidney transplantation in the future and suffer fewer stone events, perhaps with less strict therapeutic regimens. Pharmacological compounds directly inhibiting GO or LDH are also under development and could be of special interest in developing countries where RNAi therapies may not be readily available in the near future. Approaches to manipulate the intestinal microbiome with a goal to increase oxalate degradation or to stimulate secretion of oxalate into the intestine from plasma are also under development. Overall, we appear to be entering a new phase of PH treatment, with an array of promising approaches emerging that will need optimization and evaluation to establish long-term efficacy and safety.

Keywords: glycolate oxidase, hyperoxaluria, LDH-A, paediatrics, RNA interference

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INTRODUCTION

Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disease caused by mutations in the *AGXT* gene, which encodes the hepatic peroxisomal enzyme alanine–glyoxylate aminotransferase (AGT) [1]. Defects in AGT increase glyoxylate and oxalate production, the latter inducing kidney stones and nephrocalcinosis because of its low solubility when it combines with calcium within the kidney. Genotype/phenotype correlations have been described, but symptoms and age at diagnosis vary dramatically from severe infantile forms that lead to kidney failure during the first months of life [2] to forms that present in adulthood with moderate to advanced chronic kidney disease (CKD), including kidney failure, nephrocalcinosis and recurrent bilateral kidney stones [1].

Until very recently, treatment of PH1 was supportive, consisting of intensive hyperhydration and use of crystallization inhibitors including potassium citrate and neutral phosphorus [3]. Vitamin B6 (pyridoxine), a co-factor to AGT, can effectively reduce oxalate generation in a subset of PH1 patients who are partially responsive depending on their underlying genotype [2–4]. However, only approximately 20–30% of PH1 patients are B6 responsive, and pyridoxine does not affect oxalate generation in PH2 and PH3. Among PH patients who reach kidney failure, intensive (often daily) haemodialysis is required to reduce the risk of systemic oxalosis. Combined or sequential liver/kidney transplantation has been the preferred therapy, since kidney transplant alone is frequently followed by rapid loss of the allograft due to calcium oxalate crystal deposition [1, 4]. Thus, the quality of life of PH patients can be greatly impacted by their disease, even when successfully treated. Furthermore, combined kidney liver transplant is associated with a significant risk of morbidity and mortality.

The generation of oxalate in the liver and absorption from the intestine are described in Figure 1. In both instances, oxalate enters the bloodstream and must be eliminated by the kidneys, since humans have no enzyme to degrade oxalate. Calcium oxalate crystals can form within the kidney, increasing the risk for calcium oxalate kidney stones or, when hyperoxaluria is extreme, result in oxalate nephropathy.

Oxalate metabolism in the liver is complex (Figure 2). Novel therapies based on RNA interference (RNAi) have recently emerged to modulate these pathways: the main principle is to induce depletion of substrate for enzymes upstream to decrease/avoid oxalate production. RNAi molecules interfere with the biological process of transcription/translation of specific messenger RNA molecules via the unique sequence of the targeted message. Andrew Fire and Craig C. Mello shared the 2006 Nobel Prize in Physiology and Medicine for their work on RNAi in the nematode worm *Caenorhabditis elegans*, which they published in 1998 [5]. Since the discovery of RNAi and its regulatory potentials, it has become evident that RNAi has immense potential for suppressing specific targeted genes. RNAi is now known to be precise, efficient, stable and better than antisense therapy for gene suppression. The liver is a particularly attractive therapeutic target since particles containing the RNAi can be coated with molecules that efficiently promote hepatic endocytosis. One of the first RNAi applications was the development of patisiran for hereditary transthyretin amyloidosis in 2013 [6]. Since then, RNAi technology has been extensively explored in the field of orphan diseases that involve hepatic overproduction of pathogenic molecules, for example, not only for genetic hypercholesterolaemia and acute hepatic porphyria [7, 8], but also for more common diseases including hyperlipidaemia via targeting low-density lipoprotein cholesterol [9].

In PH1, two hepatic enzymes have been targeted to decrease/avoid oxalate production: glycolate oxidase (GO) with lumasiran and lactate dehydrogenase (LDH-A) with nedosiran (Figure 2). Mannose/N-acetyl glucose amine residues on the hepatic asialoglycoprotein receptor specifically bind the drug, minimizing off-target effects and maximizing delivery to the liver after subcutaneous injection [10]. Lumasiran was approved in 2020 by both the European Medicines Association (product number EMEA/H/C/005040) and the US Food and Drug Administration (reference 4706370) for patients with PH1 [11]. Clinical trials with nedosiran for all three forms of PH are ongoing.

The aim of this review is to summarize the current knowledge on RNAi therapies in PH1 and to also discuss other therapeutic possibilities in the field.

LUMASIRAN

Lumasiran targets mRNA of the *HAO1* gene encoding hepatic GO, with a goal to decrease endogenous production of oxalate by the liver. The first experimental data in the murine model of PH1 were published in 2017 [12], demonstrating a significant dose-dependent decrease of urinary oxalate (UOx) in an *agxt* knockout mouse model when lumasiran (then named ALN-GO1) was administered, with a parallel increase in urinary glycolate. This raised the question of whether high glycolate levels in the liver, blood or kidney could be toxic to humans. To date, evidence to answer this important question is limited. A healthy adult woman in her fifth decade was identified with a homozygous frameshift mutation of the *HAO1* gene in a large genetic dataset of an autozygous human population [13]. Follow-up investigation demonstrated that although her plasma glycolate concentrations were more than 12 times the upper normal limit (UNL) and urine glycolate excretion was 6 times the UNL, yet she was overall quite healthy with no overt clinical phenotype [13].

To date, phase 1 and 2 studies of lumasiran have been reported in 32 healthy subjects and 20 adults and children with PH1, with a good safety profile [14]. In a recently published 6-month double-blind phase 3 study (ILLUMINATE-A) conducted in a cohort of 39 PH1 patients aged 6 years or older with an estimated glomerular filtration rate (eGFR) $\geq$30 mL/min/1.73 m^2 and 24-h UOx $\geq$0.70 mmol/day/1.73 m^2 were randomized 2:1 to lumasiran or placebo [15]. The primary endpoint was the percent change in 24-h UOx excretion from baseline to Month 6. Secondary endpoints included the percent change in the plasma oxalate level from baseline to Month 6 and the percentage of patients with a 24-h UOx excretion no greater than 1.5 times the UNL at Month 6. The least-squares mean difference in the change in 24-h UOx excretion (lumasiran minus placebo) was −53.5% ($P < 0.001$), with a 65.4% reduction in the lumasiran group. An effect was seen as early as Month 1. The between-group differences for all hierarchically tested secondary endpoints were significant. The difference in the percent change in the plasma oxalate level (lumasiran minus placebo) was −39.5% ($P < 0.001$). In the lumasiran group, 84% of patients had 24-h UOx excretion no higher than 1.5 times the UNL at Month 6, compared with 0% in the placebo group ($P < 0.001$). Mild, transient injection-site reactions were reported in 38% of

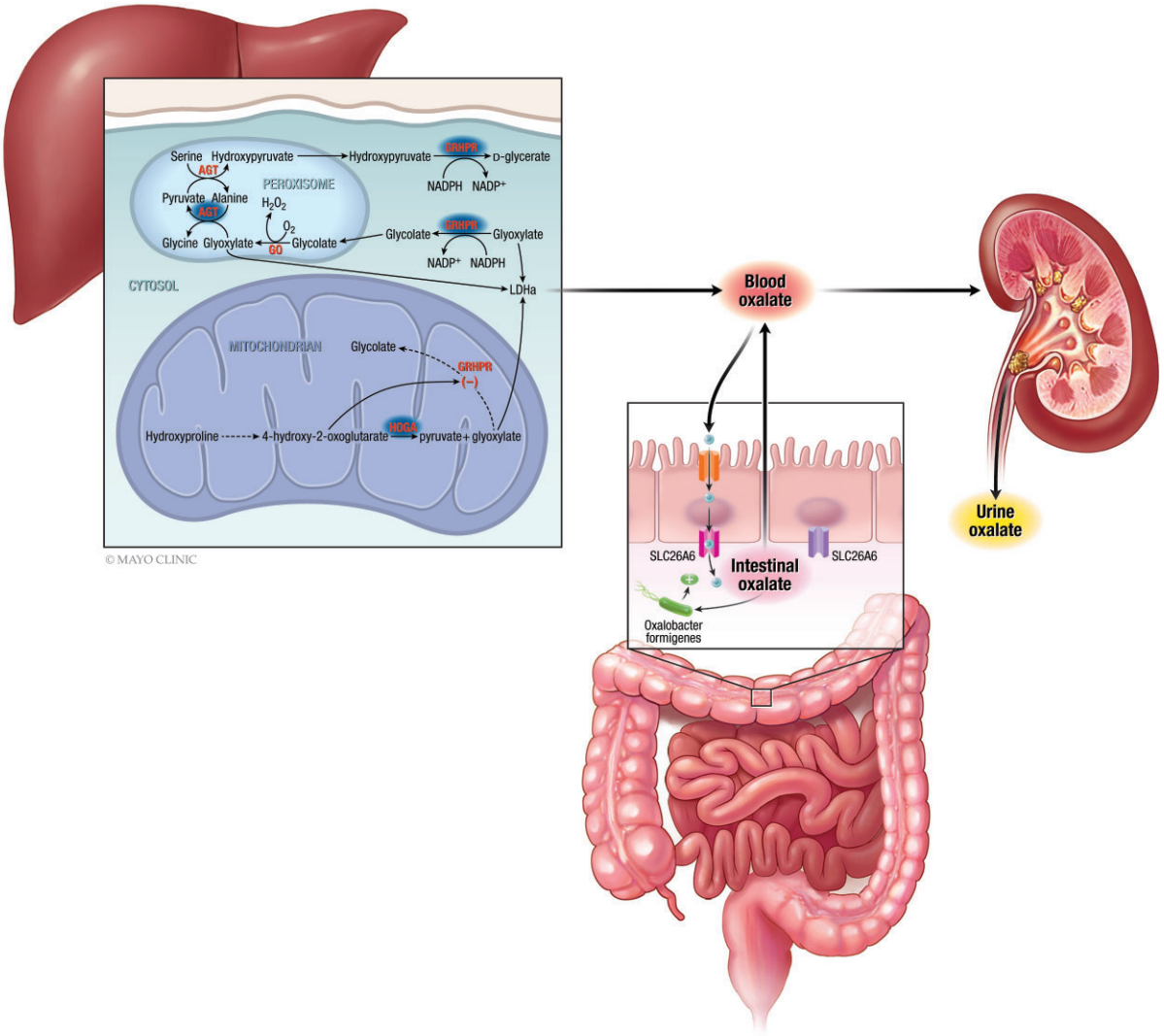

FIGURE 1: Generation and elimination of oxalate and potential therapeutic targets. Oxalate in the blood is derived from hepatic metabolism and absorption from the gastrointestinal tract. Since humans possess no enzyme to degrade oxalate, oxalate that enters the bloodstream must be eliminated by the kidney. Within tubular fluid, oxalate can combine with calcium to make relatively insoluble calcium oxalate crystals that, in turn, can result in calcium oxalate kidney stones or severe oxalate nephropathy. Mutations in three enzymes have been associated with hepatic overproduction of oxalate: *AGXT* that encodes peroxysomal alanine glyoxylate transferase (PH1), cytosolic *GR/HPR* that encodes glyoxylate reductase/hydroxy pyruvate reductase (PH2) and *HOGA1* that encodes mitochondrial 4-hydroxy-2-oxoglutarate aldolase (PH3). Defects in all three genes are thought to lead to increased production of glyoxylate, which, in turn, is converted by the hepatic isoform of LDH-A into oxalate. However, recent evidence suggests that the pathways involved in oxalate generation in PH2 may be more complicated. In addition, the pathways that lead from HOG malfunction to oxalate generation are also incompletely understood, but may involve GR/HPR inhibition within mitochondria, with the net effect of excess glyoxylate generation, which, in turn, can be converted into oxalate. The majority of oxalate from the diet is felt to be absorbed passively with paracellular transport. However, experimental evidence also suggests that oxalate can be actively secreted by intestinal cells. *In vitro* animal studies suggest that the oxalate-degrading bacteria *Oxalobacter formigenes* secretes a soluble factor that can stimulate luminal secretion of oxalate via SLC26A6. Work is ongoing to better understand these pathways and identify other factors that might increase active oxalate secretion into the gut. Other bacteria within the intestinal microbiome can also potentially degrade oxalate; thus, work is ongoing to determine whether or not manipulation of intestinal oxalate degradation could be employed to either reduce oxalate absorption from the diet or increase secretion from the bloodstream.

lumasiran-treated patients [15]. Results of the ILLUMINATE-B (children <6 years of age) and ILLUMINATE-C (patients with eGFR ≤45 or kidney failure) have not yet been published.

NEDOSIRAN

LDH-A inhibition by RNAi to prevent glyoxylate-to-oxalate conversion has emerged as the second potential therapeutic option for all types of PH because of the very downstream position of LDH in the oxalate metabolic pathway (Figure 2). The PHYOX-1 study, a randomized, single-ascending-dose, phase 1 study, was performed to evaluate safety, pharmacokinetics, pharmacodynamics and effects on oxalate metabolism of subcutaneous nedosiran in 25 healthy controls and 18 patients with PH1 or PH2. A mean maximum reduction in 24-h UOx of 55% at Day 57 was observed in adults and a total of 67% of patients reached normal or near-normal 24-h UOx in this trial [16]. Since LDH-A is expressed in the liver and muscles, there was some concern as to whether this approach could have extrahepatic side effects in muscle. Preclinical data in mice and non-human primates demonstrated that LDH-A inhibition by RNAi reduced UOx

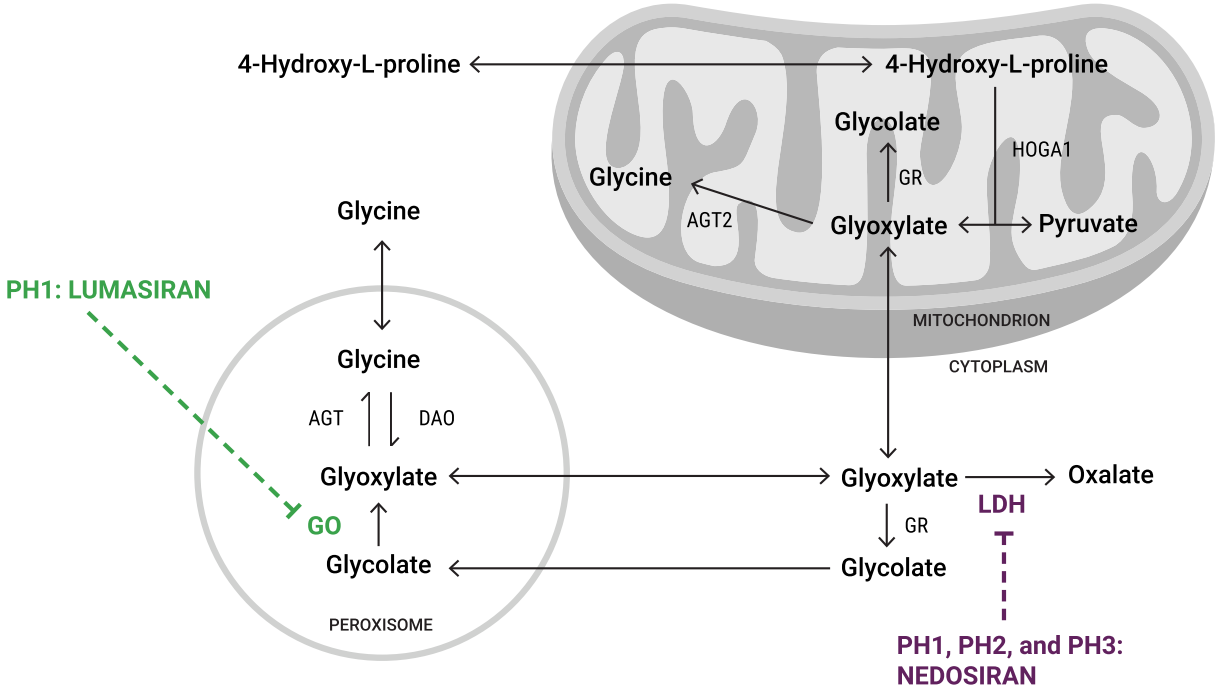

FIGURE 2: Liver metabolism of oxalate and targets of the novel RNAi therapies. GO, glycolate oxidase; LDH, lactate dehydrogenase; AGT, alanine: glyoxylate aminotransferase; DAO, D-amino oxidase; GR, glyoxylate reductase; HOGA, 4-hydroxy-2-oxoglutarate aldolase. Oxalate metabolism in the liver is complex. Novel therapies based on RNAi have recently emerged to modulate these pathways: the main principle is to induce depletion of substrate for enzymes upstream to decrease/avoid oxalate production. The liver is a particularly attractive therapeutic target, since particles containing RNAi can be coated with molecules that efficiently promote hepatic endocytosis. In PH1, two hepatic enzymes have been targeted to decrease/avoid oxalate production: GO with lumasiran and LDH-A with nedosiran. Mannose/N-acetyl glucose amine residues on the hepatic asialoglycoprotein receptor (Gal-NAc) can rapidly and specifically bind the RNAi-containing particles, thus minimizing off-target effects and maximizing delivery to the liver after a subcutaneous injection.

excretion. Via the use of a GalNac tag, effects were liver-specific with no off-target effects in other tissues observed, including in muscle [17]. Reported cases of human LDH-A deficiency describe a phenotype that lacks significant muscular manifestations, and healthy volunteers in the phase 1 PHYOX-1 study experienced no drug-related musculoskeletal adverse events. Furthermore, no significant alterations in plasma lactate, pyruvate or creatine kinase concentrations were reported in the nedosiran group as compared with the placebo group [17]. Thus, evidence to date suggests that the use of nedosiran to target hepatic LHD-A is a safe and promising approach for all forms of PH. However, phase 3 placebo-controlled double-blind studies in PH1 and PH2 are ongoing and results are pending.

QUESTIONS THAT REMAIN OPEN REGARDING USE OF RNAi IN PH

Although results of the clinical trials performed in the field of PH1 with RNAi appear especially promising and may indeed be a real 'game changer', some questions remain unanswered. First, clinical trials have largely described effects on the surrogate biomarker UOx. Although retrospective observational studies suggest that lower UOx excretion is associated with decreased risk of kidney failure [18], long-term prospective data in PH1 patients treated with lumasiran are not yet available. Thus, far longer follow-up data are needed to determine whether RNAi therapies can delay (and ideally prevent) kidney failure in PH1 patients. Long-term safety data are also not yet available, but the use of other RNAi therapies in other orphan diseases has been well tolerated for almost 8 years. The potential efficacy of lumasiran to prevent, delay or reverse oxalosis in PH1 patients with CKD also remains to be determined, although the ongoing ILLUMINATE-C clinical trial may answer some of these questions. For example, will PH1 patients treated with lumasiran still require intensive dialysis (4 or more times a week)? Can they receive a kidney transplant alone, instead of a kidney and liver transplant? What level of plasma oxalate would be needed to proceed with a kidney transplant without a concurrent liver transplant? And last, but not least, will the cost of novel RNAi limit their availability in real life?

OTHER THERAPEUTIC PERSPECTIVES

Small molecule therapies

Stiripentol, a pharmacological agent that inhibits LDH and is already approved for Dravet syndrome (a rare genetic epileptic encephalopathy) in the USA and Europe, appears a promising potential therapy for PH in both animal models and pilot human studies [19]. However, some authors have challenged this observation [20, 21], and clinical trials are ongoing to prove its efficacy in PH1. Other small molecules are in the pipeline, including oral small molecule inhibitors to LDH or GO, or chaperones for misfolded enzymes to restore function, but these remain at the stage of pre-clinical experimentation [22, 23].

Intestinal degradation of oxalate

The oxalate-metabolizing bacterium *Oxalobacter formigenes* has also been extensively studied within the last decade to see whether it could mediate active elimination of oxalate from the

plasma to the intestine of PH patients, thereby reducing UOx in patients with PH1. However, a few well-designed clinical trials have been performed in this setting, with discrepant but overall negative results [24–26].

It appears that *Oxalobacter* secretes a factor that enhances intestinal oxalate secretion (Figure 1). This is a potential strategy to eliminate oxalate from the bloodstream in an extrarenal manner. Preclinical research is ongoing to identify the factor and potentially develop compounds that act similarly and could potentially be employed in humans [27]. Enzymes that can degrade oxalate and be administered orally, such as oxalate decarboxylase, could exert an effect within the gastrointestinal lumen. The use of such oral enzymes might represent an alternative strategy to eliminate oxalate from the intestine and also create gradients that stimulate oxalate secretion from the blood [28].

Targeted gene therapy

Another therapeutic possibility in the field of PH1 could be a targeted gene therapy with human-induced pluripotent stem cells using CRISPR/Cas9 technology. A proof of concept study has indeed shown that a CRISPR/Cas9-mediated integration of an *AGXT* minigene in patient-specific iPSCs could be an efficient strategy to generate functionally corrected hepatocytes, which in the future may serve as a source for an autologous cell-based gene therapy for the treatment of PH1 [29]. Another way to use the CRISPR/Cas9 technology for PH1 would be via inhibition of LDH or GO. Although this option is currently under consideration by at least one biotech company, clinical data are not available.

CONCLUSION

Results with the two RNAi therapies currently available (lumasiran) or in later stage trials (nedosiran) appear to significantly reduce UOx in PH1 patients, but long-term data on efficacy (preservation of kidney function and improvement of stones events), as well as safety, remain to be established. These therapies thus bring great hope to families and PH1 patients, with the potential to avoid the need for double liver/kidney transplantation in the future and even possibly avoid the need for kidney transplantation if RNAi are initiated early in the disease course. As always in the case of molecularly targeted therapies developed for rare diseases, the price may ultimately limit availability. Thus already available or yet to be developed oral agents, such as stiripentol, could be of special interest in certain populations or geographic regions.

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