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Editorial Comment

EDITORIAL COMMENT

Primary hyperoxaluria type 1: time for prime time?

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ABSTRACT

Oxalate crystals in the kidney were first described in 1925. Since then, many major milestones have been reached in the understanding of genetic primary hyperoxaluria(s). Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disease due to a mutation in the *AGXT* gene, which encodes the hepatic peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), inducing excess oxalate production and further kidney stones, nephrocalcinosis and chronic kidney disease (CKD). Symptoms and age at diagnosis of PH1 vary dramatically, from the most severe infantile forms leading to end-stage kidney disease (ESKD) during the first months of life to the less severe adult forms with moderate CKD and recurrent kidney stones. In 2020, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved a therapy based on RNA interference (RNAi) that profoundly reduces endogenous oxalate synthesis and dramatically changes the treatment algorithm for patients with PH1. The aim of this supplement of *Clinical Kidney Journal* includes contemporary reviews of the pathophysiology and genetics, (conventional) medical therapeutic management, urological therapeutic management and novel therapies (including not only RNAi, but also other therapeutic perspectives). The specific opinions of both adult and paediatric nephrologists will be compared and the ethical issues, as well as challenges faced by physicians and patients in developing countries, will also be discussed. Despite all the accomplishments, there are still looming questions that require further investigation and discovery.

Keywords: hyperoxaluria, nephrocalcinosis, nephrolithiasis, oxalate, RNAi

Oxalate crystals in the kidney were first described by the French urologist C. Lepoutre in the French Academy of Medicine in 1925. In 2020, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved a therapy that profoundly reduces endogenous oxalate synthesis and dramatically changes the treatment algorithm for those afflicted with primary hyperoxaluria type 1 (PH1). PH1 is an autosomal recessive disease due to a mutation in the *AGXT* gene that encodes the hepatic peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT) [1]. Defects in AGT profoundly increase oxalate production, the latter inducing kidney stones, nephrocalcinosis and further chronic kidney disease (CKD). Genotype/phenotype correlations have been described, but symptoms and age at diagnosis vary dramatically [2], from the most severe infantile forms leading to end-stage kidney disease (ESKD) during the first months of life to the less severe adult forms with moderate CKD and recurrent kidney stones [1].

Between 1925 and 2021, many major milestones have been reached, as profiled in Figure 1. These include better insights into the pathophysiology and several improvements in the management of patients afflicted with this severe orphan disease. Pyridoxine (vitamin B6) sensitivity in some forms of

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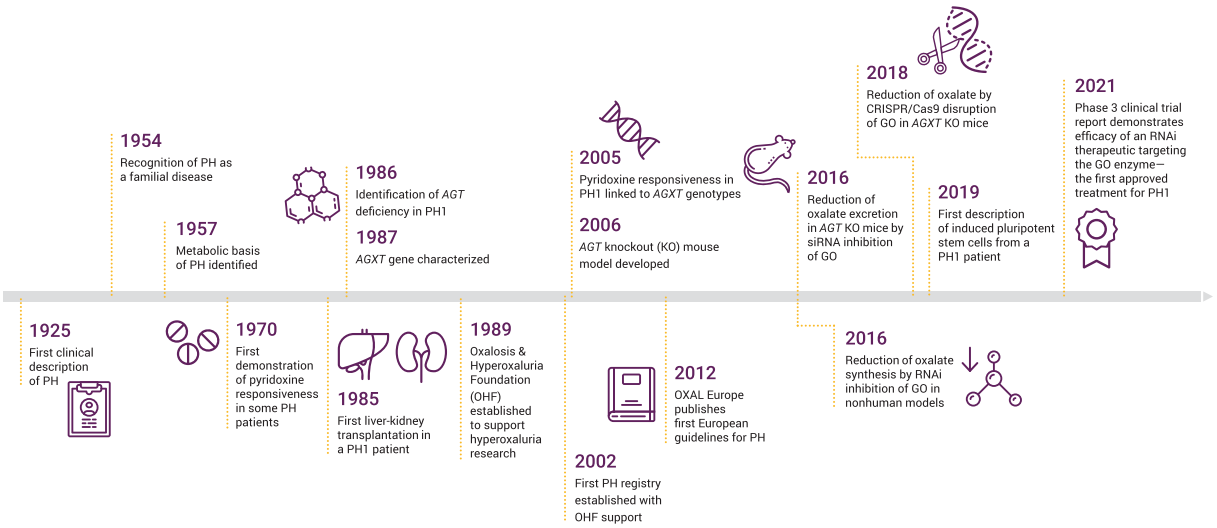

FIGURE 1: Historical milestones in primary hyperoxaluria type 1.

primary hyperoxaluria was first described in 1969 [3], well before the demonstration that PH1 was a peroxisomal disease due to decreased activity of the peroxisomal alanine-glyoxylate aminotransferase in hepatocytes from two patients, as compared with five healthy controls [4]. Even before this pathophysiological explanation, some authors had already proposed combined kidney/liver transplantation in PH1, unfortunately with a fatality from generalized cytomegalovirus infection in the first patient [5]. Later on, pre-emptive liver transplantation and liver cell transplantation were proposed [6, 7]. The murine model of PH1 was described in 1999 [8], and in 2006 adenoviral gene therapy was proven to be effective in this model [9]. In parallel, scientific networks and patients' associations emerged, on both sides of the Atlantic Ocean, with the Oxalosis and Hyperoxaluria Foundation (OHF) in the USA and OxalEurope in Europe. This led to the development of clinical registries, which dramatically improved our knowledge of epidemiology and clinical course of the disease, notably by dissecting the clinical course of not only PH1 but also the other two subtypes currently known, PH2 and PH3 [10–13]. Clinical guidelines have also been proposed to guide the diagnosis and management of PH1 patients [14], and these are being currently updated to incorporate utilization of some of the recently introduced novel therapies.

Before 2020, management of patients with PH1 consisted of intensive hydration, urine alkalinization and CKD management [15], and vitamin B6 in patients with specific mistargeting gene mutations [2, 14, 15]. Among patients who reach ESKD, intensive daily haemodialysis should be performed before proceeding to combined or sequential liver/kidney transplantation [1, 14]. Patients undergoing transplantation are at risk of not only severe perioperative complications, but also the long-term consequences of immunosuppression. Novel therapies based on RNA interference (RNAi) of glycolate oxidase (GO) (lumasiran) and lactate dehydrogenase A (nedosiran) have recently emerged and aimed at attenuating hepatic oxalate synthesis in PH1 [16, 17]. Lumasiran was approved in 2020 by both the EMA and the FDA [18], and nedosiran is currently being evaluated for FDA approval. These therapies are a real game changer for managing those with PH1, likely improving quality of life and potentially preventing the need for transplantation.

This supplement of *Clinical Kidney Journal* includes contemporary reviews of the pathophysiology and genetics, (conventional) medical therapeutic management, urological therapeutic management and novel therapies (including not only RNAi, but also other therapeutic perspectives). The specific opinions of both adult and paediatric nephrologists will be compared and the ethical issues, as well as challenges faced by physicians and patients in developing countries, will also be discussed.

Despite all the accomplishments, there are still looming questions that require further investigation and discovery. Answering these questions should pave the way for better treatment of patients afflicted with PH1, PH2, PH3 and perhaps other yet to be identified subtypes.

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CONFLICT OF INTEREST STATEMENT

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